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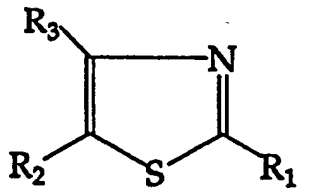
(54) Title: SUBSTITUTED THIAZOLE SULFONAMIDES AS ANTIGLAUCOMA AGENTS

(57) Abstract

The present invention provides novel carbonic anhydrase inhibitors represented by structural formula (I) wherein R_1 is: $-SO_2NH_2$; $-S(O)_nR_4$; $-C(O)R_4$; $-OR_4$; phenyl, heteroaryl, aralkyl, heteroaralkyl, aralkenyl or heteroaralkenyl having from 5 to 6 atoms in the aromatic moiety and 1 to 2 carbon atoms in the alkyl or 2 carbon atoms in the alkenyl moiety; alkyl having from 1 to 8 carbon atoms, or alkenyl or alkynyl having from 2 to 8 carbon atoms which can optionally be substituted with one or more hydroxy or carboxy groups, wherein R_4 is: hydrogen; alkyl having from 1 to 6 carbon atoms or alkenyl or alkynyl having from 2 to 6 carbon atoms; alicyclic having from 3 to 6 carbon atoms; lower carbalkoxyalkyl; phenyl; lower dialkylamino optionally further substituted by dimethylamine; or saturated nitrogen-containing heterocycles containing from 5 to 7 atoms optionally substituted with alkyl having from 1 to 3 carbon atoms and n is 0, 1 or 2; R_2 is: $-SO_2NH_2$; $-S(O)_nR_4$; $-C(O)R_4$; $-OR_4$; hydrogen; bromo; chloro; aryl or heteroaryl having from 5 to 6 atoms; alkyl having from 1 to 8 carbon atoms, or alkenyl or alkynyl having from 2 to 8 carbon atoms which can optionally be substituted with one or more hydroxy groups wherein R_4 and n are as defined above; R_3 is: hydrogen; alkyl of 1 to 6 carbon atoms; carboxy; lower carboxy alkyl; or phenyl optionally mono- or di-substituted with lower alkoxy, fluoro, chloro, bromo or alkyl of 1 to 3 carbon atoms; or R_2 and R_3 taken together form a ring fused with the 4-5 positions of the thiazole ring and are chosen from the group consisting of tetrahydrobenzene, tetrahydropyridine and thiopyran and can optionally be substituted by carboxylic acid, lower alkyl esters of carboxylic acid, lower alkyl, or halogen; provided that at least one of R_1 and R_2 must represent the sulfonamide moiety, $-SO_2NH_2$.



(I)

SUBSTITUTED THIAZOLE SULFONAMIDES AS ANTIGLAUCOMA AGENTS

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to substituted thiazolesulfonamides that have carbonic anhydrase inhibition (CAI) activity and are useful as anti-glaucoma agents.

BACKGROUND OF THE ART

Glaucoma is an ocular disorder associated with elevated intraocular pressures which are too high for normal function and may result in irreversible loss of visual function. If untreated, glaucoma may eventually lead to blindness. Ocular hypertension, i.e., the condition of elevated intraocular pressure without optic nerve head damage or characteristic glaucomatous visual field defects, is now believed by many ophthalmologists to represent the earliest phase of glaucoma.

Many of the drugs formerly used to treat glaucoma proved not entirely satisfactory. Indeed, few advances were made in the treatment of glaucoma since pilocarpine and physostigmine were introduced. Only recently have clinicians noted that many β-adrenergic blocking agents are effective in reducing intraocular pressure, they also have other characteristics, e.g. membrane stabilizing activity, that are not acceptable for chronic ocular use. (S)-1-tert-Butylamino-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol, a β-adrenergic blocking agent, was found to reduce intraocular pressure and to be devoid of many unwanted side effects associated with pilocarpine and, in addition, to possess advantages over many other β-adrenergic blocking agents, e.g., to be devoid of local anesthetic properties, to have a long duration of activity, and to display minimal tolerance.

Although pilocarpine, physostigmine and the β-adrenergic blocking agents mentioned above reduce intraocular pressure, none of these drugs manifests its action by inhibiting the enzyme carbonic anhydrase and,

thereby, impeding the contribution to aqueous humor formation made by the carbonic anhydrase pathway.

Agents referred to as carbonic anhydrase inhibitors, block or impede this inflow pathway by inhibiting the enzyme, carbonic anhydrase. While such carbonic anhydrase inhibitors are now used to treat intraocular pressure by oral, intravenous or other systemic routes, they thereby have the distinct disadvantage of inhibiting carbonic anhydrase throughout the entire body. Such gross disruption of a basic enzyme system is justified only during an acute attack of alarmingly elevated intraocular pressure, or when no other agent is effective.

Topically effective carbonic anhydrase inhibitors are reported in U.S. Patent Nos. 4,386,098; 4,416,890; and 4,426,388. The compounds reported therein are 5 (and 6)-hydroxy-2-benzothiazolesulfonamides and acyl esters thereof. Furthermore, U.S. Patent 4,544,667 discloses a series of benzofuran-2-sulfonamides, and U.S. Patent Nos. 4,477,466; 4,486,444; 4,542,152; and 4,585,787 disclose 5-phenylsulfonylthiophene-2-sulfonamides and 5-benzoylthiophene-2-sulfonamides and alkanoyloxy derivatives thereof which are reported to be topically effective carbonic anhydrase inhibitors useful in the treatment of elevated intraocular pressure (IOP) and glaucoma.

Additionally, U.S. Patent No. 4,914,111 reports that thiophene or furan-2-sulfonamides, having a 4-benzyl substituent are effective for the topical treatment of elevated intraocular pressure and glaucoma. And another application assigned to Allergan by the same inventor (07/939,189, filed 7/2/92) describes the preparation and utility of 3-thiophenesulfonamide compounds in the treatment of elevated intraocular pressure (IOP) and glaucoma.

Finally, US Patent No. 2,994,701 discloses 2-sulfamyl-4-substituted thiazoles having diuretic activity on systemic administration.

In view of the above, it is clear that a great deal of research has been carried out on the use of sulfonamides for the topical treatment of glaucoma. However, the use of the substituted 2- and 5-thiazole

sulfonamides has not been suggested for use in the topical treatment of glaucoma.

Therefore, one object of this invention is to provide novel substituted 2- and 5-thiazole sulfonamides.

It is another object of this invention to provide compounds having carbonic anhydrase inhibition activity.

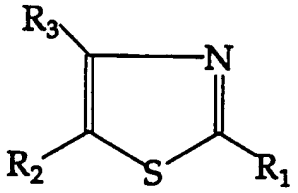
Another object of this invention is to provide a method of inhibiting carbonic anhydrase activity to thereby treat elevated intraocular pressure (IOP) and glaucoma.

A further object of this invention is to provide CAI inhibitory compounds which have little or cysteine reactivity and hence little sensitization potential when administered to the eye.

Other objects and advantages of the instant invention will become apparent from a careful reading of the specification below.

SUMMARY OF THE INVENTION

The present invention provides novel compounds having carbonic anhydrase inhibition activity and useful in the treatment of glaucoma. These compounds are represented by the structural formula:



wherein R_1 is: $-SO_2NH_2$; $-S(O)_nR_4$; $-C(O)R_4$; $-OR_4$; phenyl, heteroaryl, aralkyl, heteroaralkyl, aralkenyl or heteroaralkenyl having from 5 to 6 atoms in the aryl moiety and 1 to 2 carbon atoms in the alkyl or 2 carbon atoms in the alkenyl moiety; alkyl having from 1 to 8 carbon atoms, or alkenyl or alkynyl having from 2 to 8 carbon atoms which can optionally be substituted with one or more hydroxy or carboxy groups

wherein R_4 is: hydrogen; alkyl having from 1 to 6 carbon atoms or alkenyl or alkynyl having from 2 to 6 carbon atoms optionally substituted by dimethylamine; alicyclic having from 3 to 6 carbon atoms; carbalkoxyalkyl having 1 to 4 carbon atoms in the carbonyl moiety and from 1 to 6 carbon atoms in the alkoxy moiety; phenyl; $CH_3OCH_2OCH_2$; lower dialkylamino optionally further substituted by dimethylamine; or saturated nitrogen-containing heterocycles containing from 5 to 7 atoms optionally substituted with alkyl having from 1 to 3 carbon atoms and n is 0, 1 or 2;

R_2 is: $-SO_2NH_2$; $-S(O)_nR_4$; $-C(O)R_4$; $-OR_4$; bromo; chloro; aryl or heteroaryl having from 5 to 6 atoms; alkyl having from 1 to 8 carbon atoms, or alkenyl or alkynyl having from 2 to 8 carbon atoms which can optionally be substituted with one or more hydroxy groups wherein R_4 and n are as defined above;

R_3 is: hydrogen; alkyl of 1 to 6 carbon atoms; carboxy; lower carboxy alkyl; or phenyl optionally mono- or di-substituted with lower alkoxy, fluoro, chloro, bromo or alkyl of 1 to 3 carbon atoms; or R_2 and R_3 taken together form a ring fused with the 4-5 positions of the thiazole ring and are chosen from the group consisting of tetrahydrobenzene, tetrahydropyridine and thiopyran and can optionally be substituted by carboxylic acid, lower alkyl or benzyl esters of carboxylic acid, lower alkyl, or halogen;

provided that at least one of R_1 and R_2 must represent the sulfonamide moiety, $-SO_2NH_2$.

These compounds when applied to the eye of a patient in need of such treatment reduce the elevated intraocular pressure of glaucoma and so can prevent or retard the sight-threatening sequelae of this condition.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

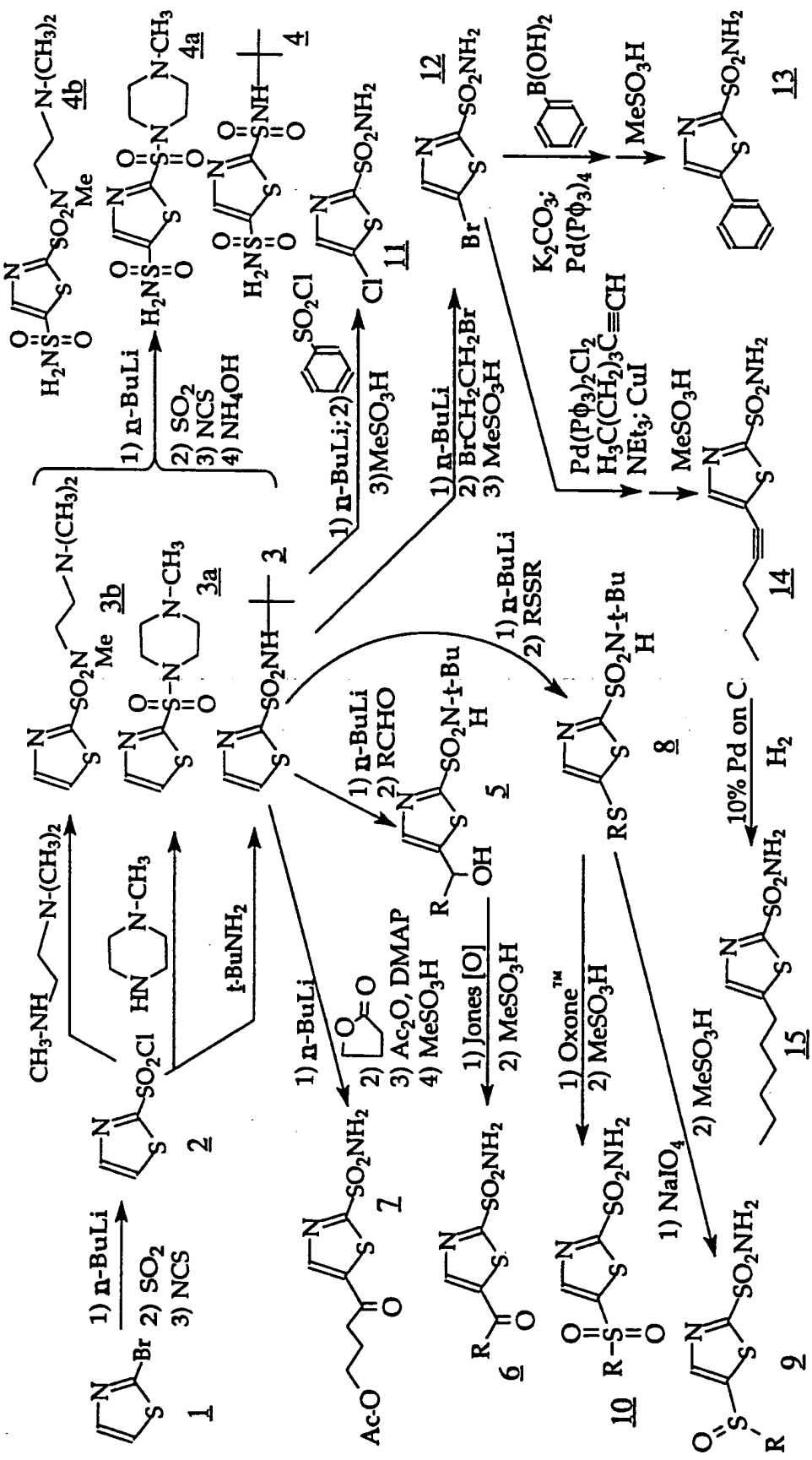
Lower alkyl is accorded the meaning of 1 to 6 carbon aliphatic chains that are straight or branched, unless otherwise defined when used, in a similar fashion lower alkenyl or lower alkynyl are accorded the meaning of 2 to 6 carbon atom chains that are straight or branched.

A primary sulfonamide group is the sulfonamide moiety without substitution of the nitrogen atom attached to the SO_2 group, i.e. $-SO_2NH_2$.

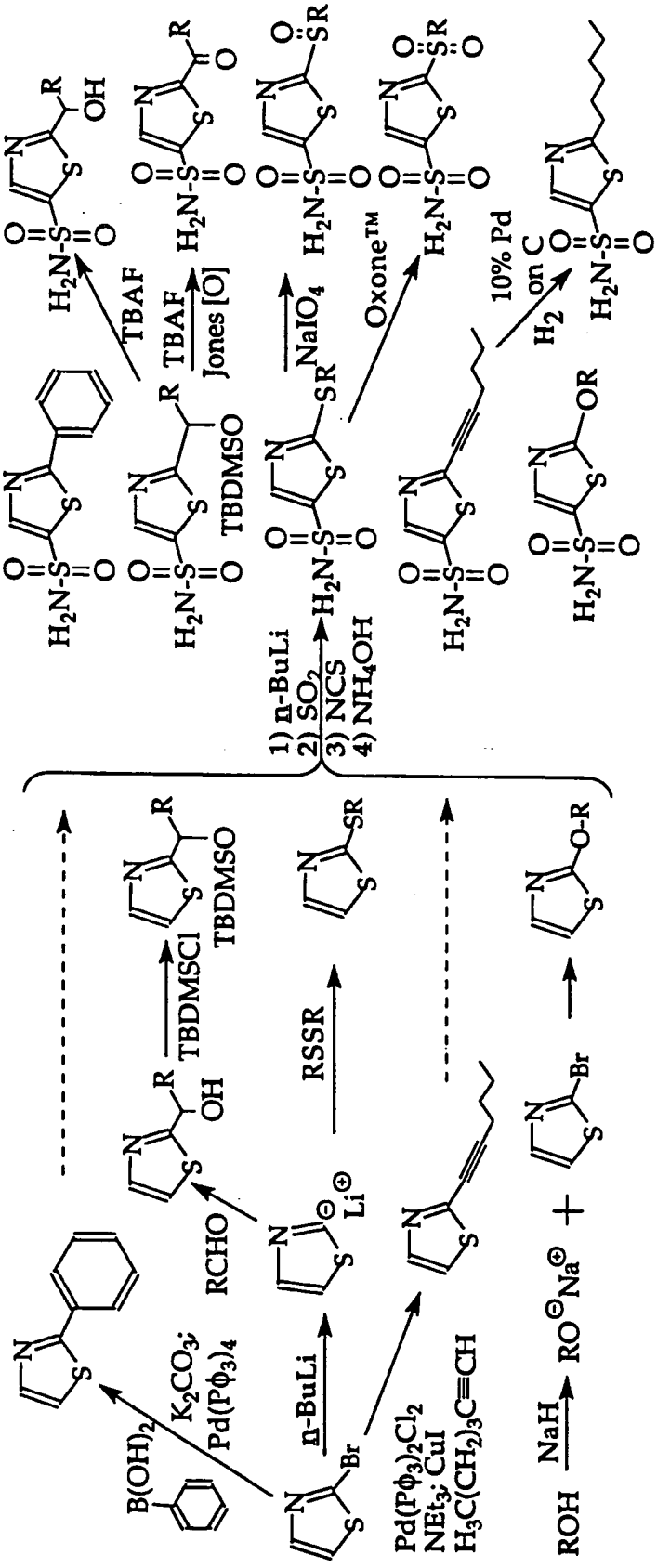
A pharmaceutically acceptable salt may be prepared for any compound made in accordance with this invention, provided the compound has a functionality capable of forming such salt, for example an acid or an amine functionality. A pharmaceutically acceptable salt may be any salt which retains the activity of the parent compound and does not impart any deleterious or untoward effect on the subject to which it is administered and in the context in which it is administered. Such a salt may be derived from any organic or inorganic acid or base. The salt may be a mono or polyvalent ion. Of particular interest where the acid function is concerned are the inorganic ions, sodium, potassium, calcium, and magnesium. Organic amine salts may be made with amines, particularly ammonium salts such as mono-, di-, and trialkyl amines or ethanol amines. Salts may also be formed with caffeine, tromethamine and similar molecules. Where the nitrogen is sufficiently basic as to be capable of forming acid addition salts, such may be formed with any suitable inorganic or organic acids. Preferred salts are those formed with inorganic acids such as hydrochloric acid, sulfuric acid or phosphoric acid.

Abbreviations used in schemes 1, 2 and 3 below represent the following reagents or variables: n-BuLi = n-butyl lithium; NCS = N-chlorosuccinimide; NH_4OH = ammonium hydroxide; t-$BuNH_2$ = tert. butylamine; Ac = acetate; Ac_2O = acetic anhydride; DMAP = dimethylamino pyridine; $MeSO_3H$ = methanesulfonic acid; in RCHO, R can be phenyl or lower alkyl optionally substituted with hydroxy or silylated hydroxy; Jones oxidation is CrO_3 in pyridine; in RSSR, R can be phenyl or lower alkyl optionally substituted with hydroxy or silylated hydroxy; Oxone™ = potassium peroxymonosulfate complex; $Pd(P\phi_3)_2Cl_2$ = bis(tri-phenylphosphine) palladium chloride; $Pd(P\phi_3)_4$ = tetrakis(triphenylphosphine) palladium (0); NEt_3 = triethylamine; CuI = copper (I) iodide; $NaIO_4$ = sodium periodate; and 10% Pd on C = 10% palladium on carbon, TBDMSCl = tertiary butyldimethylsilyl chloride.

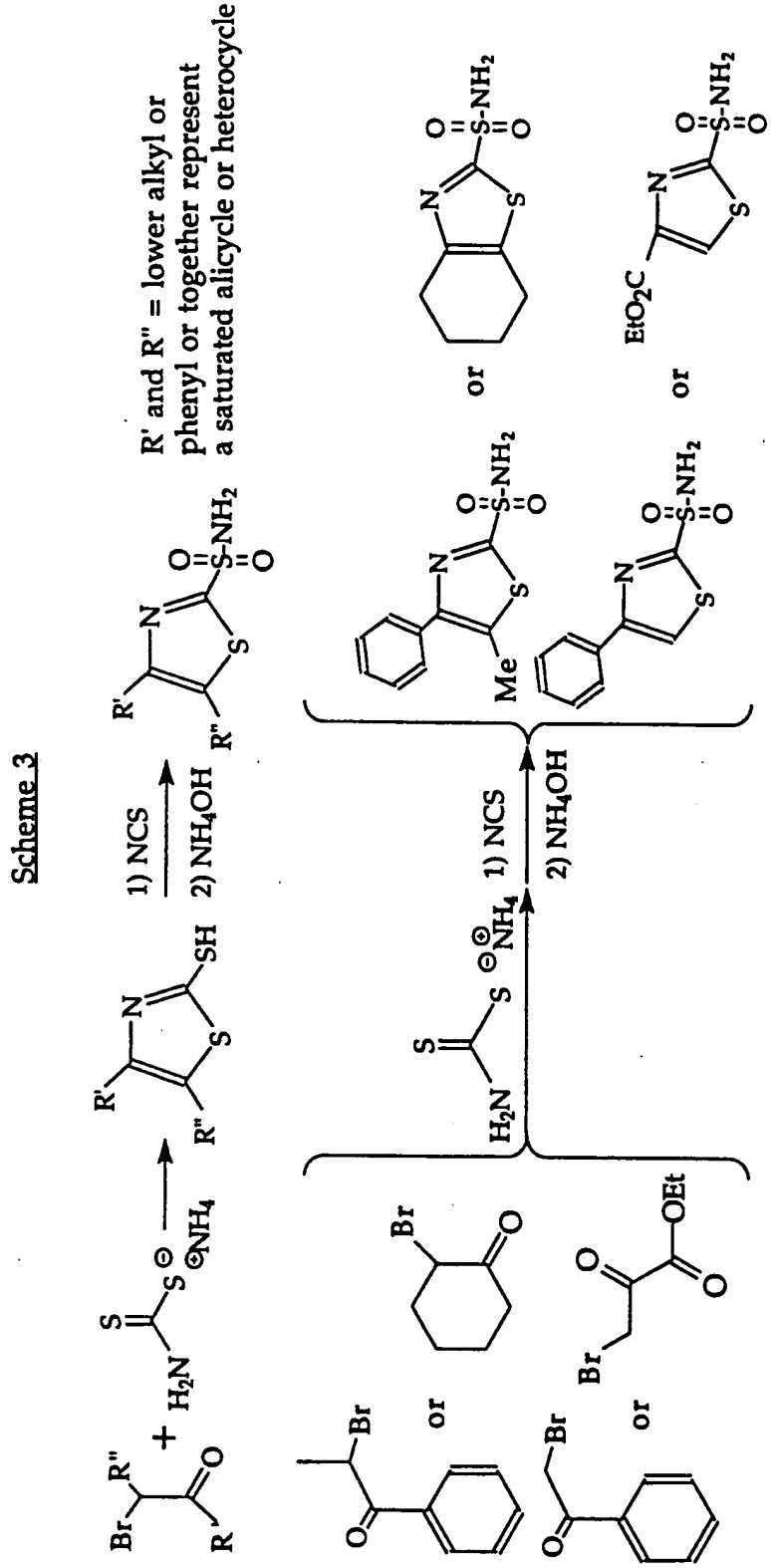
Scheme 1


1) n-BuLi
2) SO2
3) NCS
CH3-NH-N-(CH3)2
HN N-CH3
t-BuNH2
1) n-BuLi
2) RCHO
1) n-BuLi
2) RSSR
1) n-BuLi
2) BrCH2CH2Br
3) MeSO3H
1) n-BuLi; 2)
3)MeSO3H
1) n-BuLi
2) Ac2O, DMAP
3) MeSO3H
4) MeSO3H
1) Jones [O]
2) MeSO3H
1) Oxone™
2) MeSO3H
1) NaIO4
2) MeSO3H
10% Pd on C
H2
K2CO3;
Pd(Pφ3)4
Pd(Pφ3)2Cl2
H3C(CH2)3C≡CH
NEt3; CuI
MeSO3H
1) n-BuLi
2) SO2
3) NCS
4) NH4OH
1 2 3 4 4a 4b 5 6 7 8 9 10 11 12 13 14 15

Scheme 2


B(OH)2
K2CO3;
Pd(Pφ3)4
n-BuLi
Br
Pd(Pφ3)2Cl2
NEt3; CuI
H3C(CH2)3C≡CH
ROH
NaH
RO⊖Na⊕
RCHO
Li⊕
RSSR
TBDMSCl
TBDMSO
OH
1) n-BuLi
2) SO2
3) NCS
4) NH4OH
H2N-S=O
TBAF
Jones [O]
NaIO4
Oxone™
10% Pd
on C
H2
OR
O-R
SR

Scheme 3


R' and R" = lower alkyl or phenyl or together represent a saturated alicycle or heterocycle
1) NCS
2) NH4OH
or
Me
EtO2C

Specific Embodiments

The novel compounds of the invention may be prepared by the methods outlined in the preceding schemes, 1, 2 and 3.

In the formation of 2-sulfonamido-5-thiazole sulfonamides as shown in Scheme 1, 2-bromothiazole (1) is reacted with n-BuLi in tetrahydrofuran at a temperature of about -78° C. Into this solution containing the lithio-thiazole anion is then added sulfur dioxide gas (SO_2) at the same reduced temperature. After the sulfinate salt is formed, and warming to room temperature, the solvent is removed, and the residue is resuspended in dichloromethane at ambient temperature and N-chlorosuccinimide is added to form the 2-thiazole sulfonyl chloride (2). The 2-thiazole sulfonyl chloride (2), which can be isolated in crude form after filtration and stripping off solvent, can be reacted with a variety of alkyl amines or secondary nitrogen containing heterocycles to form substituted sulfonamides as shown in the next step of Scheme 1, such as 2(N-t-butylsulfamyl)-thiazole sulfonamide (3) and related compounds (3a and 3b).

Treatment of the N-substituted 2-thiazole sulfonamides (3, 3a, 3b) with n-BuLi, in tetrahydrofuran at about -78° C gives the 5-lithio thiazole anion which when treated with sulfur dioxide gas (SO_2) at the same reduced temperature forms another sulfinate salt. After warming to room temperature, the solvent is removed, and the residue is resuspended in dichloromethane at ambient temperature and N-chlorosuccinimide is added to form the 5-thiazole sulfonyl chloride intermediate. Treatment of this intermediate compound with concentrated aqueous ammonium hydroxide yields the 5-sulfamyl compounds which correspond to 4, 4a, 4b.

2(N-t-butylsulfamyl)-thiazole sulfonamide (3) is useful as an intermediate in preparing 5-substituted 2-thiazole sulfonamides by a variety of electrophilic addition reactions. The lower half of Scheme 1 illustrates some of the reactions that are encompassed in this class of addition reactions. Reaction of 2(N-t-butylsulfamyl)-thiazole sulfonamide (3) with n-BuLi, in tetrahydrofuran at about -78° C generates the 5-lithio thiazole anion which is reactive with a variety of electrophiles in the

same low temperature range, including aldehydes, disulfides and γ-butyrolactone. Reaction of 3 with an aldehyde gives a hydroxy compound 5 which can be converted to the primary sulfonamide by elimination of 2-methylpropene in a halogenated polar solvent with a boiling point between 75° C and 120° C with methanesulfonic acid or another strong organic acid. Alternatively, the hydroxy compound 5 can be oxidized to a ketone by treatment with Jones reagent or a similar oxidizing agent, and similarly the protecting t-butyl group can be removed from the sulfonamide moiety by treatment with methanesulfonic acid at reflux in a high boiling point halogented solvent to give compounds of formula 6.

Reaction of 5-lithio thiazole anion with disulfides in tetrahydrofuran at about -78° C affords the sulfide products represented by structure 8, which can generate the primary sulfonamide moiety by reflux in dichloromethane with methanesulfonic acid or another strong organic acid. Treatment of 8 with a mild oxidizing agent such as sodium periodate in a polar, protonated solvent, such as water at ambient temperature yields the sulfinate compounds (after removal of the t-butyl group by the standard method) corresponding to 9. Treatment of 8 with a stronger oxidizing agent such as Oxone™ (potassium peroxymonosulfate complex) in a polar, protonated solvent, such as water, or a water and ethanol mixture, at ambient temperature yields the sulfone compounds (after removal of the t-butyl group by the standard method) corresponding to 10.

Reaction of 5-lithio thiazole anion with γ–butyrolactone in tetrahydrofuran at about -78° C gives the acylated product, 5-(4-hydroxybutanoyl)-2-thiazole sulfonamide the hydroxy function of which can be acetylated with acetic anhydride to provide the product 7, after elimination of the t-butyl group.

The 5-lithio thiazole anion can also be used to generate the 5-bromo (and chloro)-2-thiazole sulfonamides (11, 12) by reaction with suitable halogen sources such as benzenesulfonyl chloride or dibromoethane.

The brominated 2-thiazole sulfonamide is a useful intermediate in the formation of other 5-substituted compounds by catalyzed linking reactions. Reaction of 12 with phenyl boronic acid in the presence of

tetrakis(triphenylphosphine) palladium(0) and potassium carbonate yields the 5-phenyl substituted compound, 13. And the catalyzed reaction of 12 and hexyne in the presence of bis(triphenylphosphine)palladium chloride with cuprous iodide and triethylamine provides the 5-hexynyl substituted compound, 14, which can subsequently be reduced to the 6-hexyl group, 15, using hydrogen and 10% palladium on carbon.

Scheme 2 outlines methods of making 2-substituted-5-thiazole sulfonamides which are analogous to the methods outlined in scheme 1 for making 5-substituted-2- thiazole sulfonamides. The same reagents and substantially the same starting materials are employed, only the order of introduction of substituents is altered. Starting with the 2-bromothiazole, the electrophilic addition of the variable substituent is effected first, and thereafter treatment of these 2-substituted intermediates with n-butyl lithium, sulfur dioxide , N-chlorosuccinimide, and ammonium hydroxide provides the sulfonamide moiety at the 5 position of the thiazole ring.

Scheme 3 demonstrates the method of making 4-substituted, 4 and 5-substituted, and the fused-ring compounds of the invention. Generally, these compounds can be synthesized by the cyclization of an α-bromo ketone compound with ammonium dithiocarbamate. The cyclized intermediate produced is the 4, or 4 and 5 substituted 2-thiazole thiol. Oxidation of the thiol with N-chlorosuccinimide and treatment of with concentrated ammonium hydroxide yields representative compounds of the reaction such as 4-phenyl-5-methyl-2-thiazole sulfonamide (16), 2-sulfamyl-4,5,6,7-tetrahydrobenzothiazole (17), 4-phenyl-2-thiazole sulfonamide (18) and 2-sulfamyl-4-carboxyethylthiazole (19).

In terms of inhibition activity of the carbonic anhydrase enzyme, preferred compounds of the invention are the 5-substituted-2-thiazole sulfonamides and the 2-substituted-5-thiazole sulfonamides where the substituents are as described in the Summary of the Invention. Inhibition activities of examples of compounds of the invention can be seen in Table 1, below. Particularly preferred are those compounds that have an IC_{50} (concentration at which 50% of enzyme is inhibited) value of 15 or less.

An additional measurement made on some compounds of the invention is the cysteine reactivity. This reactivity measurement gives an indication of the likelihood that a compound will react with cysteine residues in the eye, and so is a measure of the likelihood of development of sensitization in the eye to that compound. More particularly preferred are those compounds which exhibit little or no cysteine reactivity. In general, substituents that are more highly electron withdrawing, such as sulfonyl or carbonyl moieties adjacent to the thiazole ring, increase cysteine reactivity. Still more particularly preferred are those compounds with an IC_{50} of 15 or less that also are not cysteine reactive, or have low cysteine reactivity.

When administered for the treatment of elevated intraocular pressure of glaucoma, the active compound is most desirably administered topically to the eye, although systemic treatment is also satisfactory.

When given systemically, the drug can be given by any route, although the oral route is preferred. In oral administration the drug can be employed in any of the usual dosage forms such as tablets or capsules, either in a contemporaneous delivery or sustained release form. Any number of the usual excipients or tableting aids can likewise be included.

The active drug of this invention is most suitably administered in the form of ophthalmic pharmaceutical compositions adapted for topical administration to the eye such as a suspension, ointment, or as a solid insert. Formulations of these compounds may contain from 0.01 to 15% and especially 0.5% to 3% of medicament. Higher dosages as, for example, about 10%, or lower dosage can be employed provided the dose is effective in reducing or controlling elevated intraocular pressure. As a unit dosage from 0.001 to 10.0 mg, preferably 0.005 to 2.0 mg, and especially 0.1 to 1.0 mg of the compound is generally applied to the human eye, generally on a daily basis in single or divided doses so long as the condition being treated exists.

The herein before described dosage values are believed accurate for human patients and are based on the known and presently understood pharmacology of the compounds, and the activity of other similar entities

in the human eye. As with all medications, dosage requirements are variable and must be individualized on the basis of the disease and the response of the patient.

The pharmaceutical preparation which contains the active compound may be conveniently admixed with a non-toxic pharmaceutical organic carrier. Typical of pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or aralkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally employed acceptable carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl alcohol, buffering ingredients such as sodium chloride, sodium borate, sodium acetate, and other conventional ingredients such as sorbitan monolaurate, polyoxyethylene sorbitan monopalmitylate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetraacetic acid, and the like. Additionally, suitable ophthalmic vehicles can be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems, isotonic boric acid vehicles, isotonic sodium chloride vehicles, isotonic sodium borate vehicles and the like. The pharmaceutical preparation may also be in the form of a solid insert.

While many patients find liquid medication to be entirely satisfactory, others may prefer a solid medicament that is topically applied to the eye, for example, a solid dosage form that is suitable for insertion into the cul-de-sac. To this end the carbonic anhydrase inhibiting agent can be included with a non-bioerodable insert, i.e., one which after dispensing the drug remains essentially intact, or a bioerodable insert, i.e., one that either is soluble in lachrymal fluids, or otherwise disintegrates.

For example, one may use a solid water soluble polymer as the carrier for the medicament. The polymer used to form the insert may be any water soluble non-toxic polymer, for example, cellulose derivatives such as methylcellulose, sodium carboxymethyl cellulose, or a hydroxy lower alkyl cellulose such a hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose and the like; acrylates such as polyacrylic acid salts, ethyl acrylates, polyacrylamides; natural products such as gelatin, alginates, pectins, tragacanth, karaya, chondrus, agar, acacia; the starch derivatives such as starch acetate, hydroxyethyl starch ethers, hydroxypropyl starch, as well as other synthetic derivatives such as polyvinyl alcohol, polyvinyl pyrrolidone, polyvinyl methyl ether, polyethylene oxide, neutralized carbopol and xanthan gum, and mixtures of said polymers.

The invention is further illustrated by the following examples which are illustrative of a specific mode of practicing the invention and is not intended as limiting the scope of the appended claims.

Example 1:

2-N-t-butyl thiazole sulfonamide (3)

To a solution of 2-bromothiazole (9.1g, 56mmol) in 224mL of ethyl ether, cooled to -78°C, was added dropwise n-butyllithium (1.6M, 34.7 mL, 56 mmol) . The solution was stirred under argon at -78°C for 60 min. An excess of SO_2 was bubbled through the reaction. The reaction was slowly warmed to room temperature and then concentrated under reduced pressure. The crude product was added to 224mL of dichloromethane. N-chlorosuccinamide (8.2g, 61.6mmol) was added and the reaction stirred at room temperature for 3 min. The mixture was filtered and the filtrate collected and concentrated under reduced pressure. To the crude product in 130mL of THF was added 30mL of t-butylamine. The reaction was stirred at room temperature overnight and then diluted with water and extracted with ethyl acetate. The organic phase was washed with 1N HCl, water and then brine. The solvent was removed under reduced pressure and the product recrystallized from hexane/ethyl acetate. 7.5g (34,3mmol, 62%) of 2-N-t-butyl thiazole sulfonamide (white crystals) was recovered.

^{1}H NMR $(CD_3)_2CO$:

7.98 (d, J= 3 Hz, 1H), 7.95 (d, J= 3 Hz, 1H), 7.00 (bs, 1H), 1.28 (s, 9H)
^{13}C NMR $(CD_3)_2CO$:
169.48, 144.40, 125.71, 55.34, 30.04

Example 2:
2-Thiazole sulfonamide

To a solution of 2-N-t-butylthiazole sulfonamide (0.1g, 0.45mmol) in 5mL of 1,2-dichloroethane was added methanesulfonic acid (69mL, 1.1mmol). The reaction was heated at reflux for 8h and then concentrated under reduced pressure. The product was subjected to flash chromatography (1:1 hexane/ethyl acetate). 57mg (0,35mmol, 78%) of 2-thiazole sulfonamide (white solid) was recovered.

^{1}H NMR $(CD_3)_2CO$:
7.98 (d, J= 3.1 Hz, 1H), 7.94 (d, J= 3.1 Hz, 1H), 7.26 (bs, 2H)
^{13}C NMR $(CD_3)_2CO$:
169,31, 144.69, 125.48
Mass Spect.:
EI - 164 (M^+)
High Res.:
Calcd. 163.9214
Found 163.9221
Elemental Analysis:
Calcd. C 21.95, H 2.44, N 17.07
Found C 22.10, H 2.26, N 17.10

Example 3:
5-Benzoyl-2-thiazole sulfonamide

To a solution of 2-N-t-butylthiazole sulfonamide (0.5g, 2.3mmol) in 23mL of ethyl ether, cooled to -78°C, was added n-butyllithium (1.26M, 3.65mL, 4.6mmol). The reaction was stirred under argon at -78°C for 1h. Benzaldehyde (0.26mL, 2.53mmol) was added and the reaction was stirred at room temperature (rt) overnight. Saturated ammonium chloride was added to quench the reaction. The mixture was extracted with ethyl acetate and the organic phase washed with water (3X) followed by brine. The solvent was removed under reduced pressure and the product

subjected to flash chromatography (2:1 hexane/ethyl acetate). 0.35g of the benzhydrol compound and 0.19g of 2-N-t-butylthiazole sulfonamide were recovered.

To a solution of the benzhydrol compound (0.1g, 0.31mmol) in 3mL of acetone was added Jone's reagent (2.67M, 0.12mL, 0.31mmol). The reaction was stirred at room temperature (rt) for 5 min and then quenched with isopropyl alcohol. The mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed with water followed by brine. The solvent was removed under reduced pressure to afford 94mg of the benzoyl compound.

To a solution of the benzoyl compound (0.1g, 0.31mmol) in 5mL of 1,2-dichloroethane was added methanesulfonic acid (60mL, 0.93mmol). The reaction was heated at reflux for 2h and then concentrated. The product was subjected to flash chromatography (3:2 hexane/ethyl acetate). 61mg (0.23mmol, 74%) of 5-benzoyl-2-thiazole sulfonamide (white crystals) was recovered.

^{1}H NMR $(CD_3)_2CO$:

8.46 (s, 1H), 7.97-8.00 (m, 2H), 7.72-7.77 (m, 1H), 7.60-7.65 (m, 2H), 7.52 (bs, 2H)

^{13}C NMR $(CD_3)_2CO$:

187.26, 174.15, 149.28, 143.43, 137.76, 134.34, 130.07, 129.76

Mass Spect.:

EI - 268 (M^+)

High Res.:

Calcd. 267.9976

Found 267.9968

Elemental Analysis:

Calcd. C 44.76, H 3.00, N 10.44

Found C 44.90, H 2.74, N 10.29

Example 4:

5-Chloro-2-thiazole sulfonamide (11)

To a solution of n-butyllithium (1.6M, 2.84mL, 4.6mmol) in 15mL of ether at -78°C was added 2-N-t-butylthiazole sulfonamide (0.5g, 2.3mmol) in 10mL of ethyl ether. The reaction was stirred under argon at -78°C for 1h. Benzene sulfonyl chloride (0.30mL, 2.3mmol) was added and

the reaction was stirred at rt for 30 min. Saturated ammonium chloride was added to quench the reaction. The solution was diluted with ethyl acetate and the organic phase washed with water (3X) followed by brine. The solvent was removed under reduced pressure and the product subjected to flash chromatography (5:1 hexane/ethyl acetate). 0.34g of 5-chloro-2-N-t-butyl thiazole sulfonamide was recovered.

To a solution of 5-chloro-2-N-t-butyl thiazole sulfonamide (0.1g, 0.40mmol) in 10mL of 1,2-dichloroethane was added methanesulfonic acid (78mL, 1.2mmol). The reaction was heated at reflux for 3h and then concentrated. The product was subjected to flash chromatography (3:2 hexane/ethyl acetate). 64mg (0.3 mmol, 80%) of 5-chloro-2-thiazole sulfonamide (white crystals) was recovered.

^{1}H NMR $(CD_3)_2CO$:
7.94 (s, 1H), 7.39 (bs, 2H)
^{13}C NMR $(CD_3)_2CO$:
167.77, 143.22, 132.03
Mass Spect.:
EI - 198 (M^+)
High Res.:
Calcd. 197.9324
Found 197.9318
Elemental Analysis:
Calcd. C 18.14, H 1.52, N 14.10
Found C 18.38, H 1.45, N 14.03

Example 5:
5-(Phenylthio)-2-thiazole sulfonamide

To a solution of n-butyllithium (1.6M, 1.7mL, 2.8mmol) in 25mL of ether at -78°C was added 2-N-t-butylthiazole sulfonamide (0.3g, 1.4mmol) in 5mL of ethyl ether. The reaction was stirred under argon at -78°C for 1h. Phenyl disulfide (0.30g, 1.4mmol) in 5mL of ethyl ether was added and the reaction was stirred at -78°C for 30 min. Water was added to quench the reaction. The solution was diluted with ethyl acetate and the organic phase washed with water (3X) followed by brine. The solvent was removed under reduced pressure and the product subjected to flash chromatography (4:1 hexane/ethyl acetate). 0.20g of 5-(phenylthio)-2-N-t-

butyl thiazole sulfonamide and 0.06g of 2-N-t-butylthiazole sulfonamide were recovered.

To a solution of 5-(phenylthio)-2-N-t-butyl thiazole sulfonamide (0.14g, 0.43mmol) in 10mL of 1,2-dichloroethane was added methanesulfonic acid (84mL, 1.29mmol). The reaction was heated at reflux for 5h and then concentrated. The product was subjected to flash chromatography (2:1 hexane/ethyl acetate). 97mg (0.36mmol, 84%) of 5-(phenylthio)-2-thiazole sulfonamide (off-white solid) was recovered.

^{1}H NMR $(CD_3)_2CO$:
8.05 (s, 1H), 7.34-7.44 (m, 7H)
^{13}C NMR $(CD_3)_2CO$:
172.12, 149.21, 136.25, 135.87, 130.76, 130.59, 129.05
Mass Spect.:
EI - 273 (MH^+)
High Res.:
Calcd. 271.9748
Found 271.9745
Elemental Analysis:
Calcd. C 39.71, H 2.94, N 10.29
Found C 39.90, H 2.83, N 10.21

Example 6:
5-(Phenylsulfonyl)-2-thiazole sulfonamide

To a solution of 5-(phenylthio)-N-t-butyl thiazole sulfonamide (0.2g, 0.61mmol) (Example 5) in 6mL of a 50% ethanol/water mixture was added oxone (0.6g, 1.0mmol) in 2mL of water. The reaction was stirred at rt for 7h and then quenched with sodium bicarbonate until the reaction becomes basic. The mixture was filtered and the filtrate concentrated. The product was subjected to flash chromatography (3:1 hexane/ethyl acetate). 0.18g of 5-(phenylsulfonyl)-2-N-t-butyl thiazole sulfonamide was recovered.

To a solution of 5-(phenylsulfonyl)-2-N-t-butyl thiazole sulfonamide (0.10g, 0.28mmol) in 5mL of 1,2-dichloroethane was added methanesulfonic acid (55mL, 0.84mmol). The reaction was heated at reflux for 2h and then concentrated. The product was subjected to flash

chromatography (2:1 hexane/ethyl acetate). 68mg (0.22mmol, 79%) of 5-(phenylsulfonyl)-2-thiazole sulfonamide (white crystals) was recovered.

^{1}H NMR $(CD_3)_2CO$:

8.54 (s, 1H), 8.10-8.13 (m, 2H), 7.68-7.82 (m, 3H), 7.55 (bs, 2H)

^{13}C NMR $(CD_3)_2CO$:

175.44, 148.90, 144.65, 141.74, 135.50, 130.87, 128.47

Mass Spect.:

EI - 304 (M^+)

High Res.:

Calcd. 303.9646

Found 303.9671

Elemental Analysis:

Calcd. C 35.53, H 2.63, N 9.21

Found C 35.62, H 2.45, N 9.13

Example 7:

5-(Ethylthio)-2-thiazole sulfonamide

To a solution of n-butyllithium (1.6M, 1.7mL, 2.8mmol) in 10mL of ethyl ether at -78°C was added 2-N-t-butylthiazole sulfonamide (0.3g, 1.4mmol) in 5 mL of ethyl ether. The reaction was stirred under argon at -78°C for 1h. Ethyl disulfide (0.18mL, 1.4mmol) was added and the reaction was stirred at rt for 30 min. Water was added to quench the reaction. The solution was diluted with ethyl acetate and the organic phase washed with water (3X) followed by brine. The solvent was removed under reduced pressure and the product subjected to flash chromatography (3:1 hexane/ethyl acetate). 0.20g of 5-(ethylthio)-2-N-t-butyl thiazole sulfonamide and 0.11g of 2-N-t-butylthiazole sulfonamide were recovered.

To a solution of 5-(ethylthio)-2-N-t-butyl thiazole sulfonamide (0.17g, 0.61mmol) in 10mL of 1,2-dichloroethane was added methanesulfonic acid (0.12mL, 1.83mmol). The reaction was heated at reflux for 6h and then concentrated. The product was subjected to flash chromatography (2:1 hexane/ethyl acetate). 0.12g (0.54mmol, 89%) of 5-(ethylthio)-2-thiazole sulfonamide (white solid) was recovered.

^{1}H NMR $(CD_3)_2CO$:

7.88 (s, 1H), 7.27 (bs, 2H), 2.98 (q, J= 7.3 Hz, 2H), 1.29 (t, J= 7.3 Hz, 3H)

^{13}C NMR $(CD_3)_2CO$:

170.34, 147.66, 137.82, 32.74, 14.93

Mass Spect.:

EI - 224 (M^+)

High Res.:

Calcd. 223.9748

Found 223.9722

Elemental Analysis:

Calcd. C 26.79, H 3.57, N 12.50

Found C 27.14, H 3.53, N 12.35

Example 8:

5-Ethylsulfinyl-2-thiazole sulfonamide

To a solution of sodium periodate (92mg, 0.43mmol) in 2.6mL of water was added 5-(ethylthio)-2-N-t-butyl thiazole sulfonamide (0.1g, 0.36mmol). The reaction was stirred at rt for 48h. The mixture was filtered and the filtrate concentrated. The product was subjected to flash chromatography (1:1 hexane/ethyl acetate). 0.1g of 5-(ethylsulfinyl)-2-N-t-butyl thiazole sulfonamide was recovered.

To a solution of 5-(ethylsulfinyl)-2-N-t-butyl thiazole sulfonamide (0.10g, 0.34mmol) in 5mL of 1,2-dichloroethane was added methanesulfonic acid (44mL, 0.68mmol). The reaction was heated at reflux for 3.5h and then concentrated. The product was subjected to flash chromatography (1:5 hexane/ethyl acetate). 72mg (0.30mmol, 88%) of 5-ethylsulfinyl-2-thiazole sulfonamide (light yellow solid) was recovered.

^1H NMR $(CD_3)_2CO$:

8.24 (s, 1H), 7.48 (bs, 2H), 3.08-3.30 (m, 2H), 1.25 (t, J= 7.6 Hz, 3H)

Mass Spect.:

CI - 241 (MH^+)

High Res.:

Calcd. 239.9697

Found 239.9681

Elemental Analysis:

Calcd. C 25.00, H 3.33, N 11.67

Found C 25.36, H 3.32, N 11.07

Example 9:

5-(2-Hydroxyethyl)thio-2-thiazole sulfonamide

To a solution of 2-N-t-butylthiazole sulfonamide (1.0g, 4.5mol) in 40mL of ethyl ether at -78°C was added n-butyllithium (1.6M, 5.7mL, 9.0mmol). The reaction was stirred under argon at -78°C for 60 min. (2-Dimethylt-butylsiloxy)ethyl disulfide (1.74g, 4.5mmol) was added and the reaction was stirred at rt for 90 min. Water was added to quench the reaction. The solution was diluted with ethyl acetate and the organic phase washed with water (3X) followed by brine. The solvent was removed under reduced pressure and the product subjected to flash chromatography (5:1 hexane/ethyl acetate). 0.80g of 5-((2-dimethylt-butylsiloxy ethyl)thio)-2-N-t-butyl thiazole sulfonamide was recovered.

To a solution of 5-((2-dimethylt-butylsiloxyethyl)thio)-2-N-t-butyl thiazole sulfonamide (0.25g, 0.61mmol) in 6mL of 1,2-dichloroethane was added methanesulfonic acid (0.16mL, 2.44mmol). The reaction was heated at reflux for 4h and then concentrated. The product was subjected to flash chromatography (2:1 hexane/ethyl acetate). 73mg (0.32mmol, 52%) of 5-(2-hydroxyethyl)thio-2-thiazole sulfonamide (clear colorless liquid) was recovered.

^{1}H NMR $(CD_3)_2CO$:

7.86 (s, 1H), 3.78 (t, J= 10 Hz, 2H), 3.10 (t, J= 10 Hz, 3H)

^{13}C NMR $(CD_3)_2CO$:

170.2, 147.7, 138.2, 61.1, 41.3

Example 10:

5-(4-acetoxybutanoyl)-2-thiazole sulfonamide (7)

To a solution of 2-N-t-butylthiazole sulfonamide (0.5g, 2.3mol) in 23mL of THF at -78°C was added n-butyllithium (1.6M, 2.9mL, 4.6mmol). The reaction was stirred under argon at -78°C for 60 min. g-butyrolactone (0.16 mL, 2.3mmol) in 10mL of THF was added and the reaction was stirred at -78°C for 15 min. and then slowly warmed to rt and stirred overnight. The reaction was acidified with 1N HCl and then washed with water (3X) followed by brine. The solvent was removed under reduced pressure and the product subjected to flash chromatography (1:3

hexane/ethyl acetate). 0.27g of 5-(4-hydroxybutanoyl)-2-N-t-butyl thiazole sulfonamide was recovered.

To a solution of 5-(4-hydroxybutanoyl)-2-N-t-butyl thiazole sulfonamide (0.27g, 0.88 mmol) in 8.8mL of THF were added pyridine (0.14mL, 1.76mmol), 4-dimethylamino pyridine (catalytic amount) and acetic anhydride (0.17mL, 1.76mmol). The reaction was stirred at rt for overnight and then quenched with water. The organic phase was washed with water (2X) followed by brine. The solvent was removed under reduced pressure and the product subjected to flash chromatography (1:1 hexane/ethyl acetate). 0.26g of 5-(4-acetoxybutanoyl)-2-N-t-butyl thiazole sulfonamide was recovered.

To a solution of 5-(4-acetoxybutanoyl)-2-N-t-butyl thiazole sulfonamide (0.20g, 0.57mmol) in 11mL of 1,2-dichloroethane was added methanesulfonic acid (75mL, 2.44mmol). The reaction was heated at reflux for 4h and then concentrated. The product was subjected to flash chromatography (1:1 hexane/ethyl acetate). 78mg (0.27mmol, 47%) of 5-(4-acetoxybutanoyl)-2-thiazole sulfonamide (white solid) was recovered.

^{1}H NMR $(CD_3)_2CO$:

8.66 (s, 1H), 7.47 (bs, 2H), 4.11 (t, J= 6.4 Hz, 2H), 3.20 (t, J= 7.1 Hz, 2H), 2.04 (m, 2H), 1.96 (s, 3H)

^{13}C NMR $(CD_3)_2CO$:

192.97, 173.95, 176.94, 147.98, 144.08, 63.79, 36.90, 23.76, 20.70

Mass Spect.:

CI - 293 (MH^+)

High Res.:

Calcd. 292.0187

Found 309.0460 ($+NH_3$)

Elemental Analysis:

Calcd. C 36.99, H 4.11, N 9.59

Found C 37.15, H 4.27, N 9.29

Example 11:

4-Methyl-2-thiazole sulfonamide

To a solution of 4-methyl thiazole (3.0g, 0.03mol) in 300mL of ether at -78°C was added n-butyllithium (1.6M, 1.7mL, 2.8mmol). The reaction was stirred under argon at -78°C for 30 min. An excess of SO_2 was bubbled

through the reaction. The reaction was slowly warmed to rt and then concentrated under reduced pressure. The crude product was added to 300mL of dichloromethane. N-chlorosuccinamide (4.41g, 0.033mol) was added and the reaction stirred at rt for 20 min. The mixture was filtered and the filtrate collected and concentrated under reduced pressure. To the crude product in 250mL of acetone was added of concentrated ammonium hydroxide in 50mL of acetone. The reaction was diluted with water and extracted with ethyl acetate. The organic phase was washed with water (3X) and then brine. Recrystallization from hexane/ethyl acetate afforded 2.13g (12mmol, 40%) of 4-methyl-2-thiazole sulfonamide (tan crystals).

^{1}H NMR $(CD_3)_2CO$:
7.47 (s, 1H), 7.16 (bs, 2H), 2.44 (s, 3H)
^{13}C NMR $(CD_3)_2CO$:
168.01, 155.10, 120.00, 16.93
Mass Spect.:
EI - 179 (MH^+)
High Res.:
Calcd. 177.9871
Found 177.9870
Elemental Analysis:
Calcd. C 26.97, H 3.37, N 15.73
Found C 27.01, H 3.24, N 15.74

Example 12:
5-Bromo-2-thiazole sulfonamide (12)

To a solution of 2-N-t-butylthiazole sulfonamide (0.1g, 0.45mmol) in 10mL of THF, cooled to -78°C, was added n-butyllithium (1.6M, 0.57mL, 0.9mmol). The reaction was stirred under argon at -78°C for 1h. 1,2-dibromoethane (0.7mL, 8.1mmol) was added and the reaction stirred at rt overnight. The solvent was removed under reduced pressure and the product subjected to flash chromatography (4:1 hexane/ethyl acetate). 50mg of 5-bromo-2-N-t-butylthiazole sulfonamide and 63mg of 2-N-t-butylthiazole sulfonamide were recovered.

To a solution of 5-bromo-2-N-t-butylthiazole sulfonamide (50mg, 0.17mmol) in 2.5mL of 1,2-dichloroethane was added methanesulfonic acid (22mL, 0.34mmol). The reaction was heated at reflux for 75 min and

then concentrated. The product was subjected to flash chromatography (2:1 hexane/ethyl acetate). 38mg (0.16mmol, 94%) of 5-bromo-2-thiazole sulfonamide (white solid) was recovered.

^{1}H NMR $(CD_3)_2CO$:
8.02 (s, 1H), 7.39 (bs, 2H)
^{13}C NMR $(CD_3)_2CO$:
170.34, 146.4, 114.8
Mass Spect.:
EI - 242 (M^+)
High Res.:
Calcd. 241.8819
Found 241.4424
Elemental Analysis:
Calcd. C 14.81, H 1.23, N 11.52
Found C 15.00, H 1.30, N 11.46

Example 13 :

5-Methyl-4-phenyl-2-thiazole sulfonamide (16)

To a solution of ammonium dithiocarbamate (2.6g, 0.024mol) in 15mL of ethanol was added 2-bromopropiophenone (5g, 0.024mol). The reaction was stirred at rt overnight. The next morning the reaction was heated at 70°C for 6.5h. The reaction was diluted with water and the mixture filtered. The solid was recrystallized from ethanol/water to recover 1.35g of 5-methyl-2-mercapto-4-phenyl thiazole.

To a solution of 5-methyl-2-mercapto-4-phenyl thiazole (0.25g, 1.2mmol) in 18mL of water/dichloromethane (1:3) was added N-chlorosuccinamide (0.64g, 4.8mmol). The reaction was stirred at rt for 45 min. and then diluted with water. The organic phase was washed with saturated sodium bicarbonate, water (2X) and then brine. The solvent was removed under reduced pressure and the crude product dissolved into 12mL of acetone. 3mL of concentrated ammonium hydroxide in 7mL of acetone was added to the solution. The reaction was stirred at rt for 5 min.and diluted with water and extracted with ethyl acetate. The organic phase was washed with water (2X) followed by brine. The solvent was removed under reduced pressure and the product subjected to flash chromatography (2:1 hexane/ethyl acetate). A yellow solid was recovered

which upon recrystallization from hexane/ethyl acetate afforded 0.16g (0.63mmol, 53%) of 5-methyl-4-phenyl-2-thiazole sulfonamide (tan crystals).

^{1}H NMR $(CD_3)_2CO$:
7.70-7.72 (m, 2H), 7.41-7.51 (m, 3H), 7.26 (bs, 2H), 2.67 (s, 3H)
^{13}C NMR $(CD_3)_2CO$:
164.58, 152.74, 134.86, 134.82, 129.26, 129.11, 128.96, 12.85
Mass Spect.:
EI - 254 (M^+)
High Res.:
Calcd. 254.0183
Found 254.0200
Elemental Analysis:
Calcd. C 47.24, H 3.94, N 11.02
Found C 47.13, H 3.82, N 10.99

Example 14:

2-Sulfamyl-4,5,6,7-tetrahydrobenzothiazole (17)

To a solution of ammonium dithiocarbamate (1.4g, 12.4 mmol) in 25mL of ethanol was added 2-bromocyclohexanone (2.2g, 12.4mmol). The reaction was stirred at rt overnight. The next morning the reaction was heated at 70°C for 1h. The solvent was removed under reduced pressure. The product was subjected to flash chromatography (3:1 hexane/ethyl acetate) to recover a yellow solid. Recrystallization from ethyl acetate afforded 0.54g of 2-mercapto-4,5,6,7-tetrahydrobenzothiazole.

To a solution of 2-mercapto-4,5,6,7-tetrahydrobenzothiazole (0.24g, 1.4mmol) in 21mL of water/dichloromethane (1:2) was added N-chlorosuccinamide (0.75g, 5.6 mmol). The reaction was stirred at rt for 30 min. and then diluted with water. The organic phase was washed with saturated sodium bicarbonate, water (2X) and then brine. The solvent was removed under reduced pressure and the crude product dissolved into 25mL of acetone. 1mL of concentrated ammonium hydroxide was added to the solution. The reaction was stirred at rt for 5 min. and diluted with water and extracted with ethyl acetate. The organic phase was washed with water (2X) followed by brine. The solvent was removed under reduced pressure and the product recrystallized from hexane/ethyl acetate

to afford 82mg (0.38mmol, 27%) of 2-sulfamyl-4,5,6,7-tetrahydrobenzothiazole (tan crystals).

^{1}H NMR $(CD_3)_2CO$:

7.10 (bs, 2H), 2.74-2.87 (m, 4H), 1.85-1.89 (m, 4H)

^{13}C NMR $(CD_3)_2CO$:

165.00, 152.76, 135.59, 27.33, 23.96, 23.60, 23.25

Mass Spect.:

EI - 218 (M^+)

High Res.:

Calcd. 218.0184

Found 218.0172

Elemental Analysis:

Calcd. C 38.53, H 4.59, N 12.84

Found C 38.54, H 4.62, N 12.84

Example 15:

5-(1-Hexynyl)-2-thiazole sulfonamide (14)

5-bromo-2-N-t-butylthiazole sulfonamide (0.57g, 1.9mmol), triethylamine (0.32mL, 1.9mmol), copper (I) iodide (91mg, 0.48mmol) and bistriphenylphosphine palladium chloride (67mg, 0.095mmol) were added to 19mL of acetonitrile. The mixture was deoxygenated for 45min. 1-hexyne was added and the reaction heated at 55-60°C for overnight. The next morning an additional 33mg of bistriphenylphosphine palladium chloride and copper (I) iodide were added. The reaction was heated at 60°C for 2 days. The solvent was removed under reduced pressure and the product subjected to flash chromatography (3:1 hexane/ethyl acetate) to afford N-t-butyl-5-(1-hexynyl)-2-thiazole sufonamide.

To a solution of N-t-butyl-5-(1-hexynyl)-2-thiazole sufonamide in 19mL of 1,2-dichloroethane was added methanesulfonic acid (0.25mL, 0.34mmol). The reaction was heated at reflux for 75min and then concentrated. The product was subjected to flash chromatography (2:1 hexane/ethyl acetate). 88mg of 5-bromo-2-N-t-butylthiazole sulfonamide and 0.14g (0.57mmol, 30%) of 5-(1-hexynyl)-2-thiazole sulfonamide (white crystals) was recovered.

^{1}H NMR $(CD_3)_2CO$:

7.95 (s, 1H), 7.31 (bs, 2H), 2.51 (t, J= 7 Hz, 4H), 1.42-1.61 (m, 4H), 0.93 (t, J= 7 Hz, 3H)

^{13}C NMR $(CD_3)_2CO$:

167.60, 147.40, 125.32, 101.41, 69.55, 30.90, 22.54, 19.64, 13.75

Mass Spect.:

EI - 244 (M^+)

High Res.:

Calcd. 244.0340

Found 244.0352

Elemental Analysis:

Calcd. C 44.26, H 4.92, N 11.48

Found C 44.45, H 5.07, N 11.39

Example 16:

5-Hexyl-2-thiazole sulfonamide (15)

To a solution of 5-(1-hexynyl)-2-thiazole sulfonamide (0.1g, 0.41mmol) in 7mL of methanol was added 10% palladium/carbon (50mg, 50 wgt%). The reaction was shaken at rt under 30 atm of hydrogen for 24h. The next day the reaction was filtered through celite and the solvent removed under reduced pressure. ^{1}H NMR indicated the alkynyl compound was still present. The product was redissolved in 7mL of methanol and 100mg of 10% palladium/carbon was added. The reaction was shaken at rt under 40 atm of hydrogen for 24h. The next day the reaction was filtered through celite and the solvent removed under reduced pressure. The product was subjected to flash chromatography (3:1 hexane/ethyl acetate). 73mg (0.29mmol, 71%) of 5-hexyl-2-thiazole sulfonamide (white crystalline solid) was recovered.

^{1}H NMR $(CD_3)_2CO$:

7.69 (s, 1H), 1.66-1.71 (m, 2H), 1.29-1.40 (m, 8H), 0.87 (t, J= 7 Hz, 3H)

^{13}C NMR $(CD_3)_2CO$:

166.78, 146.47, 141.71, 32.25, 32.02, 29.22, 27.21, 23.09, 14.21

Elemental Analysis:

Calcd. C 43.52, H 6.49, N 11.28

Found C 43.29, H 6.26, N 11.07

Example 17:

4-Phenyl-2-thiazole sulfonamide (18)

To a solution of ammonium dithiocarbamate (2.76g, 25mmol) in 50mL of ethanol was added bromoacetophenone (5g, 25mmol). The reaction was stirred at rt overnight. The next morning the reaction was heated at 70°C for 2.5h. The reaction was diluted with water and extracted with ethyl acetate. The organic phase was washed with water (2X) followed by brine. The solvent was removed under reduced pressure. The product was dissolved in 375mL of dichloromethane/water (2:1) and N-chlorosuccinamide (13.4g, 100mmol) was added. The reaction was stirred at rt for 60 min. and then diluted with water. The organic phase was washed with water (2X) followed by brine. The solvent was removed under reduced pressure and the crude product dissolved into 250mL of acetone. 20mL of concentrated ammonium hydroxide was added to the solution. The reaction was stirred at rt for 15 min. and then diluted with water and extracted with ethyl acetate. The organic phase was washed with water (2X) followed by brine. The solvent was removed under reduced pressure and the product subjected to flash chromatography (2:1 hexane/ethyl acetate). Recrystallization from ethyl acetate/hexane afforded 0.43g (1.8mmol, 7.2%) of 4-phenyl-2-thiazole sulfonamide (white crystals).

^{1}H NMR $(CD_3)_2CO$:
8.24 (s, 1H), 8.00 (d, J= 8Hz, 2H), 7.37-7.50 (m, 5H)
^{13}C NMR $(CD_3)_2CO$:
169.18, 156.98, 134.33, 129.68, 129.60, 127.16, 118.93
Mass Spect.:
EI - 240 (M^+)
High Res.:
Calcd. 240.0027
Found 240.0029
Elemental Analysis:
Calcd. C 45.00, H 3.33, N 11.67
Found C 45.06, H 3.35, N 11.57

Example 18:

5-Phenyl-2-thiazole sulfonamide (13)

In 10mL of deoxygenated toluene was added 5-bromo-2-N-t-butylthiazole sulfonamide (0.30g, 1.0mmol), phenylboronic acid (0.12g, 1.0mmol) and potassium carbonate (0.28g, 2.0mmol) in 1.5mL of water/ethanol (2:1). The mixture was deoxygenated for 30 min.. Tetrakis(triphenylphosphine) palladium (0) was added and reaction heated at reflux for 36h. The reaction was diluted with ethyl acetate and washed with water (2X) followed by brine. The solvent was removed under reduced pressure and the product subjected to flash chromatography (3:1 hexane/ethyl acetate) to afford N-t-butyl-5-phenyl-2-thiazole sulfonamide.

To a solution of N-t-butyl-5-phenyl-2-thiazole sulfonamide (0.25g, 0.84mmol) in 17mL of 1,2-dichloroethane was added methanesulfonic acid (0.11mL, 1.68mmol). The reaction was heated at reflux for 6.5h and then concentrated. The product was subjected to flash chromatography (2:1 hexane/ethyl acetate). Recrystallization from ethyl acetate/hexane afforded 0.15g (0.63mmol, 63%) of 5-phenyl-2-thiazole sulfonamide (white crystals).

^{1}H NMR $(CD_3)_2CO$:
8.27 (s, 1H), 7.72-7.75 (m, 2H), 7.44-7.52 (m, 3H), 7.32 (bs, 2H)
^{13}C NMR $(CD_3)_2CO$:
167.54, 145.00, 140.32, 130.85, 130.27, 127.90
Mass Spect.:
EI - 240 (M^+)
High Res.:
Calcd.
Found
Elemental Analysis:
Calcd. C 45.00, H 3.33, N 11.67
Found C 44.91, H 3.29, N 11.52

Example 19:

5-(2-Carboxyethyl)thio-2-thiazole sulfonamide

To a solution of 2-N-t-butylthiazole sulfonamide (0.5g, 2.3mmol) in 23mL of THF, cooled to 0°C, was added n-butyllithium (1.6M, 2.9mL, 4.6mmol). The reaction was stirred under argon at 0°C for 30 min. Sulfur

(74mg, 2.3mmol) was added and the reaction stirred at 0°C for 1.5h. The reaction was quenched with deoxygenated water and warmed to rt. 3-Bromopropionic acid (0.35g, 2.3 mmol) and potassium carbonate (0.16g, 1.15mmol) in water were added to the reaction and stirred at rt overnight. The next day reaction was acidified with 1N HCl and extracted with ethyl acetate. The organic phase was washed with water (2X) followed by brine. The solvent was removed under reduced pressure and the product subjected to flash chromatography (15:1 dichloromethane/methanol). 0.31g of 5-(2-carboxyethyl)thio-2-N-t-butylthiazole sulfonamide was recovered.

To a solution of 5-(2-carboxyethyl)thio-2-N-t-butylthiazole sulfonamide (0.15g, 0.46mmol) in 5mL of 1,2-dichloroethane was added methanesulfonic acid (60mL, 0.92mmol). The reaction was heated at reflux for 2.5h and then concentrated. The product was subjected to flash chromatography (5:1 chloroform/methanol). 60mg (0.22mmol, 48%) of 5-(2-carboxyethyl)thio-2-thiazole sulfonamide (tan wax) was recovered.

^{1}H NMR $(CD_3)_2CO$:

7.90 (s, 1H), 7.28 (bs, 2H), 3.19 (t, J= 7 Hz, 2H), 2.65 (t, J= 7 Hz, 2H)

^{13}C NMR $(CD_3)_2CO$:

Elemental Analysis:

Calcd. C 26.86, H 3.00, N 10.44

Found C , H , N

Example 20:

5-(2-Carbomethoxyethyl)thio-2-thiazole sulfonamide

To a solution of 5-(2-carboxyethyl)thio-2-thiazole sulfonamide (42mg, 0.16mmol) in 5mL of methanol was added a 1N HCl solution in ethyl ether. The solution was concentrated under reduced pressure to afford 26mg (0.09mmol,56%) of (white solid).

^{1}H NMR $(CD_3)_2CO$:

7.93 (s, 1H), 7.31 (bs, 2H), 3.63 (s, 3H), 3.19 (t, J= 7 Hz, 2H), 2.70 (t, J= 7 Hz, 2H)

Elemental Analysis:

Calcd. C 29.78, H 3.57, N 9.92

Found C 30.08, H 3.46, N 9.75

Example 21:

5-Benzyloxycarbonyl-2-sulfamyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine

To a solution of ammonium dithiocarbamate (0.19g, 1.7mmol) in 2mL of ethanol was added 1-benzyloxycarbonyl-3-bromo-4-piperidone (0.53g, 1.7mol). The reaction was stirred at rt overnight. The next morning the reaction was heated at 75°C for 2h. The reaction was diluted with ethyl acetate and washed with saturated sodium bicarbonate, water (2X) and then brine. The solvent was removed under reduced pressure and the product subjected to flash chromatography (2:1 hexane/ethyl acetate). Crystallization from ethyl acetate/hexane afforded 0.14g of 5-benzyloxycarbonyl-2-mercapto-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine.

To a solution of 5-benzyloxycarbonyl-2-mercapto-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (0.14g, 0.46mmol) in 7.5mL of water/dichloromethane (1:3) was added N-chlorosuccinamide (0.24g, 1.84mmol). The reaction was stirred at rt for 1h and then diluted with water. The organic phase was washed with saturated sodium bicarbonate, water (2X) and then brine. The solvent was removed under reduced pressure and the crude product dissolved into 10mL of acetone. 0.5mL of concentrated ammonium hydroxide was added to the solution. The reaction was stirred at rt for 5 min. and diluted with water and extracted with ethyl acetate. The organic phase was washed with water (2X) followed by brine. The solvent was removed under reduced pressure and the product subjected to flash chromatography (1:1 hexane/ethyl acetate). 0.12g (0.34mmol, 74%) of 5-benzyloxycarbonyl-2-sulfamyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine(white solid) was recovered.

^{1}H NMR CD_3OD:

7.32-7.37 (m, 5H), 5.17 (s, 2H), 4.90 (bs, 2H), 3.83-3.86 (m, 2H), 3.31 (bs, 2H), 2.89
(bs, 2H)

Elemental Analysis:

Calcd. C 47.58, H 4.28, N 11.89

Found C 48.10, H 4.23, N 11.29

Example 22:

2-Sulfamyl-4-carboxyethylthiazole (19)

Ethylbromopyruvate (7.1 mL, 56.8 mmol) was added to a slurry of ammonium dithiocarbamate (6.25 g, 56.8 mmol) in EtOH (35 mL). The solution was stirred at rt 18 h, then heated at 70 - 80 °C for 2 h. The solution was cooled to 10 °C and water (70 mL) was added. The resulting precipitate was recrystallized from EtOH to give 0.7 g of 4-carboethoxy-2-mercapto thiazole. NCS (0.42 g, 3.17 mmol) was added to a solution of 4-carboethoxy-2-mercapto thiazole (0.15 g, 0.79 mmol) in CH_2Cl_2 (3.2 mL) and the solution layered with water (1.6 mL) and stirred for 2 h. The layers were separated and the water layer extracted with CH_2Cl_2. The combined extracts were concentrated and the residue dissolved in acetone (1 mL) and NH_4OH (1.6 mL) added. After 5 min the acetone was removed in vacuo and the residue taken up in water and extracted with EtOAc (6 x 5 mL). The combined extracts were dried ($MgSO_4$), filtered, concentrated and purified by chromatography using 35% EtOAc/hexane to give 0.1 g (54%) 4-carboethoxy-2-thiazole sulfonamide as a pale yellow solid.

^{1}H NMR $(CD_3)_2CO$:

8.65 (s, 1H), 7.43 (brs, 2H), 4.37 (q, 2H, J = 7.0 Hz), 1.36 (t, 3 H, J = 7.0 Hz)

^{13}C NMR $(CD_3)_2CO$:

171.4, 162.4, 150.0, 134.4, 63.6, 16.0

Mass Spect.:

CI - 237 (MH^+)

High Res.:

Calcd. $C_4H_5N_2O_4S_2$ 208.9690 (MH^+-C_2H_4)

Found 208.9676

Example 23:

5-Benzyl-2-thiazole sulfonamide

5-Benzyl-2-mercaptothiazole (0.5 g, 2.4 mmol) was dissolved in 9.6 mL of CH_2Cl_2 and NCS (1.33 g, 9.66 mmol) was added. The solution was layered with water (4.8 mL) and stirred at rt for for 2 hours. The material was extracted with CH_2Cl_2 and the organic layer washed with saturated $NaHCO_3$. The solvent was removed and the residue taken up in acetone (3 mL) and 5 mL NH_4OH added. After 30 min. an additional 5 mL of NH_4OH was added. After 30 minutes 10 mL of NH_4OH was added. After

2 hours 5 mL of NH_4OH was added and the reaction stirred overnight. The acetone was removed and the aqueous extracted with ethyl acetate, dried ($MgSO_4$), filtered and concentrated. The residue was subjected to flash chromatography (25% ethyl acetate/hexane) to afford 53 mg (9%) of 5-benzyl-2-thiazole sulfonamide.

^{1}H NMR $(CD_3)_2CO$:
7.77 (s, 1H), 7.33 (m, 4H), 7.28 (m, 1H), 7.14 (brs, 2H), 4.3 (s, 2H)
^{13}C NMR $(CD_3)_2SO$:
167.74, 145.85, 142.06, 140.26, 129.62, 129.30, 127.74, 33.21
Mass Spect.:
EI - 254 (M^+)
High Res.:
Calcd. 254.0183
Found 254.0175
Elemental Analysis:
Calcd. C 47.23, H 3.96, N 11.01
Found C 47.03, H 3.82, N 11.85

EXAMPLE 24:
4-(4-Methoxyphenyl)-2-thiazole sulfonamide (A)
5-Chloro-4-(4-methoxyphenyl)-2-thiazole sulfonamide (B)

4-(4-Methoxyphenyl)-2-mercaptothiazole (0.5 g, 2.24 mmol) was dissolved in 9 mL of CH_2Cl_2 and NCS (1.2 g, 8.97 mmol) was added. The solution was layered with water (4.5 mL) and stirred at rt for 2 hours. The material was extracted with CH_2Cl_2 and the organic layer washed with saturated $NaHCO_3$. The solvent was removed and the residue taken up in acetone (3 mL) and 5 mL NH_4OH added. After 15 min. the acetone was removed and the aqueous extracted with ethyl acetate, dried ($MgSO_4$), filtered and concentrated. The residue was subjected to flash chromatography (25% ethyl acetate/hexane) to afford 0.20 g of 5-Chloro-4-(4-methoxyphenyl)-2-thiazole sulfonamide (B) and 40 mg of 4-(4-methoxyphenyl)-2-thiazole sulfonamide. (A)
(A)
^{1}H NMR $(CD_3)_2CO$:

8.06 (s, 1H), 7.92 (d, 2H, J= 8.7 Hz), 7.32 (brs, 2H), 7.02 (d, J= 8.7 Hz, 2H), 3.84 (s, 3H)

^{13}C NMR $(CD_3)_2SO$:

168.86, 161.15, 156.99, 128.56, 127.06, 116.94, 114.98, 55.62

Mass Spect.:

EI - 271 (MH^+)

High Res.:

Calcd. 270.01328

Found 270.0145

Elemental Analysis:

Calcd. C 44.43, H 3.73, N 10.36

Found C 44.63, H 3.78, N 10.13

(B)

^{1}H NMR $(CD_3)_2CO$:

7.92 (d, 2H, J= 9 Hz), 7.46 (brs, 2H), 7.07 (d, J= 9 Hz, 2H), 3.87 (s, 3H)

^{13}C NMR $(CD_3)_2SO$:

165.29, 161.34, 151.70, 130.54, 125.14, 123.98, 114.80, 55.71

Mass Spect.:

EI - 305 (MH^+)

High Res.:

Calcd. 303.9743

Found 303.9761

Elemental Analysis:

Calcd. C 39.41, H 2.98, N 9.09

Found C 39.65, H 2.97, N 9.19

EXAMPLE 25:
2-Thiophenyl-5-thiazole sulfonamide

n-BuLi (2.0 mL, 3.2 mmol, 1.6 M) was added dropwise to a -78°C solution of 2-bromothiazole (0.05 g, 3.05 mmol) in dry Et_2O. After 1 h at -78°C, a solution of phenyldisulfide (0.7 g, 3.2 mmol) in dry Et_2O (6 mL) was added slowly and the solution stirred 20 min. The reaction was quenched with water, the layers separated and the aqueous extracted with EtOAc (4 x 5 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated. The crude material was purified by flash chromatography using 5% EtOAc/hexane to give 0.41 g (69%) of 2-thiophenyl thiazole as a colorless oil.

n-BuLi (2.5 mL, 3.98 mmol, 1.6 M) was added dropwise to a -78°C solution of 2-thiophenyl thiazole (0.73 g, 3.8 mmol) in dry Et_2O (10 mL). The solution turned dark brown after addition of the first few drops of n-BuLi. The solution was stirred 1 h at -78°C then SO_2 gas was bubbled over the surface of the solution for 10 min. The solution was warmed to rt, then the solvent was removed and the residue taken up in CH_2Cl_2 (10 mL) and NCS (0.53 g, 3.98 mmol) was added. After stirring at rt for 2 h, another 1.06 g NCS was added and stirring continued another 1 h. The solution was filtered and the filtrate concentrated. The residue was dissolved in acetone (5 mL) and NH_4OH (8 mL) was added. After 20 min, the acetone was removed in vacuo and the aqueous extracted with EtOAc, dried ($MgSO_4$) and concentrated. The crude material was purified using 35% EtOAc/hexane to give 0.28 g (27%) of 2-thiophenyl-5-thiazole sulfonamide as a pale yellow solid.

mp 134 -136°C

^{1}H NMR $(CD_3)_2CO$:

7.96 (s, 1H), 7.79 (m, 2H), 7.61 (m, 3H), 7.03 (brs, 2H)

^{13}C NMR $(CD_3)_2CO$:

174.9, 146.1, 141.4, 136.1, 132.1, 131.4, 130.2

Elemental Analysis:

Calcd. C 39.72, H 2.96, N 10.29

Found C 39.33, H 2.59, N 9.97

EXAMPLE 26:
2-Phenylsulfinyl-5-thiazole sulfonamide

A solution of $NaIO_4$ (0.55 g, 2.57 mmol) in water (5.7 mL) was added dropwise to a solution of 2-thiophenyl-5-thiazole sulfonamide (0.23 g, 0.86 mmol) in MeOH (14 mL) and the solution stirred 16 h. Dioxane (10 mL) was added to increase the solubility and the reaction stirred anther 48 h. The solution was filtered and the residue purified by flash chromatography using 30% EtOAc/hexane to give 0.3 g of 2-phenylsulfoxyl-5-thiazole sulfonamide.

mp 110 - 112°C

^{1}H NMR $(CD_3)_2CO$:

8.22 (s, 1H), 7.86 (m, 2H), 7.65 (m, 3H), 7.28 (br, 2H)

^{13}C NMR $(CD_3)_2CO$:

219.1, 182.8, 182.0, 179.8, 169.0, 166.4, 161.0

Mass Spect.:

288 (M^+)

High Res.:

Calcd. $C_9H_8N_2O_3S_3$ 287.9697 (M^+)

Found 287.9103

Elemental Analysis:

Calcd. C 37.49, H 2.80, N 9.71

Found C 37.77, H 2.96, N9.44

EXAMPLE 27:
2-Phenylsulfonyl-5-thiazole sulfonamide

A solution of Oxone (0.48 g, 0.77 mmol) in water (7 mL) was added dropwise to a solution of 2-thiophenyl thiazole (0.1 g, 0.5 mmol) in MeOH (7 mL) at rt. The solution was stirred at rt over night. The solution was cooled to 0°C and saturated $NaHCO_3$ was added dropwise until the solution became basic. The solids were filtered off and washed with MeOH and EtOAc. The filtrate was evaporated, the residue taken up in a minimum volume of water and extracted with EtOAc. The combined extracts were dried (Na_2SO_4) and concentrated to give 0.11 g of 2-phenysulfonyl thiazole as a white powder.

n-BuLi (0.58 mL, 0.93 mmol, 1.6 M) was added dropwise to a -78°C solution of 2-phenylsulfonyl thiazole (0.2 g, 0.89 mmol) in dry THF (2 mL). The solution turned pale yellow after addition of the first few drops of n-BuLi. The solution was stirred for 1 h at -78°C then SO_2 gas was bubbled over the surface of the solution for 10 min. The solution was warmed to rt, then the solvent was removed and the residue taken up in CH_2Cl_2 (2 mL) and NCS (0.12 g, 0.93 mmol) was added. After stirring at rt for 2 h, the solution was filtered and the filtrate concentrated. The residue was dissolved in acetone (2 mL) and NH_4OH (2 mL) was added. After 20 min., the acetone was removed in vacuo and the aqueous extracted with EtOAc, dried ($MgSO_4$) and concentrated. The crude material was purified using 35% EtOAc/hexane to give 0.14 g (50%) of 2-phenylsulfonyl-5-thiazole sulfonamide as a pale yellow solid.

mp 119 - 120°C

^{1}H NMR $(CD_3)_2CO$:

8.33 (s, 1H), 8.12 (m, 1H), 7.85 (m, 1H), 7.74 (m, 2H), 7.44 (brs, 1 H)

^{13}C NMR $(CD_3)_2CO$:

171.0, 148.6, 147.0, 138.8, 136.0, 130.7, 129.6,

Elemental Analysis:

Calcd. C 35.56, H 2.65, N 9.21

Found C 35.64, H 2.49, N 9.11

EXAMPLE 28

2-(1-Hydroxyhexyl)-5-thiazole sulfonamide

n-BuLi (4.0 mL, 6.4 mmol, 1.6 M) was added dropwise to a -78°C solution of 2-bromothiazole (1.0 g, 6.1 mmol) in dry Et_2O (12 mL). After stirring at -78°C for 1 h, hexanal (0.77 mL, 6.4 mmol) was added and the solution stirred for 30 min. before a solution of TBDMSCl (1.1 g, 7.3 mmol) in dry Et_2O (5 mL) was added. The solution was allowed to warm to rt while stirring for 16 h. The reaction was quenched with water, the layers separated and the aqueous extracted with EtOAc. The combined extracts were dried ($MgSO_4$) and condensed. The crude material was purified by flash chromatography using 30% EtOAc/hexane to give 0.70 g (62%) of 2-(1-hydroxyhexyl)thiazole.

TBDMSCl (1.37 g, 9.07 mmol) and DBU (1.4 mL, 9.07 mmol) were added to a solution of 2-(1-hydroxyhexyl)thiazole (0.7 g, 3.8 mmol) in dry THF (8 mL). The mixture was stirred at rt for 3 h, then quenched with water and the layers separated. The aqueous portion was extracted with EtOAc, the combined extracts dried ($Mg SO_4$) and concentrated. The material was purified by flash chromatography to give 1.03 g (91%) of 2-(1-trimethylsiloxyhexyl)thiazole as a pale yellow oil.

n-BuLi (1.77 mL, 2.83 mmol, 1.6 M) was added dropwise to a -78°C solution of 2-(1-trimethylsiloxyhexyl)thiazole (0.81 g, 2.7 mmol) in dry THF (2 mL). The solution was stirred 1 h at -78°C, then SO_2 gas was bubbled over the surface of the solution for 10 min. The solution was warmed to rt, then the solvent removed and the residue taken up in CH_2Cl_2 (2 mL) and NCS (0.38 g, 2.83 mmol) was added. After stirring at rt for 2 h, the solution was filtered and the filtrate concentrated. The residue was dissolved in acetone (2 mL) and NH_4OH (5.4 mL) was added. After 20 min, the acetone was removed in vacuo and the aqueous extracted

with EtOAc, dried ($MgSO_4$) and concentrated. The crude material was dissolved in THF (5 mL) and TBAF (5 mL) was added. After 30 min. the reaction was quenched with water and the layers separated. The aqueous portion was extracted with EtOAc, the combined extracts dried ($MgSO_4$), concentrated and purified by flash chromatography using 40% EtOAc/hexane to give 0.43 g (60%) of 2-(1-hydroxyhexyl)-5-thiazole sulfonamide as a white solid.

mp 139 - 141°C

^{1}H NMR $(CD_3)_2CO$:

8.03 (s, 1H), 7.03 (brs, 2H), 5.46 (brd, 1H, J = 4.5 Hz), 4.9 (m, 1H), 1.93 (m, 1H), 1.8 (m, 1 H), 1.5 (m, 2 H), 1.3 (m, 4 H), 0.87 (t, 3 H, J = 6.9 Hz)

^{13}C NMR $(CD_3)_2CO$:

183.7, 145.5, 141.5, 72.2, 38.5, 32.2, 25.2, 23.1, 14.2

Elemental Analysis:

Calcd. C 40.98, H 6.10, N 10.6

Found C 41.05, H 6.15, N10.55

EXAMPLE 29:

2-(1-Hexanoyl)-5-thiazole sulfonamide

Jones' reagent (0.14 mL, 0.38 mmol, 2.67 M) was added dropwise to a 0°C solution of 2-(1-hydroxyhexyl)-5-thiazole sulfonamide (0.08 g, 0.32 mmol) in acetone (1 mL). The ice bath was removed and the solution stirred for 30 min. The reaction was quenched with a few drops of isopropanol and the acetone removed in vacuo. The residue was taken up in water and extracted with EtOAc. The combined extracts were dried ($MgSO_4$), concentrated and recrystallized from EtOAc/hexane to give 0.031 g (38%) of 2-(1-hexanoyl)-5-thiazole sulfonamide as a white solid.

mp 124 - 125°C

^{1}H NMR $(CD_3)_2CO$:

8.34 (s, 1H), 7.35 (brs, 2H), 3.15 (t, 2H, J = 7.3 Hz), 1.73 (m, 2H), 1.37 (m, 4H), 0.89 (t, 3 H, J = 7.0 Hz)

^{13}C NMR $(CD_3)_2CO$:

194.5, 170.7, 148.3, 146.7, 38.6, 32.0, 24.1, 23.1, 14.1

Mass Spect.:

CI - 263 (MH^+)

High Res.:
Calcd. $C_9H_{14}N_2O_3S_2$ 262.0445 (M^+)
Found 262.0454
Elemental Analysis:
Calcd. C 41.20, H 5.38, N 10.68
Found C 40.99, H 5.19, N10.47

EXAMPLE 30:
2-Ethylthio-5-thiazole sulfonamide

n-BuLi (4.0 mL, 6.4 mmol, 1.6 M) was added dropwise to a -78°C solution of 2-bromothiazole (1.0 g, 6.1 mmol) in dry Et_2O (12 mL). After 1 h at -78°C, ethyldisulfide (0.79 g, 6.4 mmol) was added slowly and the solution stirred for 16 h. The reaction was quenched with water, the layers separated and the aqueous extracted with EtOAc (4 x 5 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated. The crude material was purified by flash chromatography using 5% EtOAc/hexane to give 0.55 g (62%) of 2-thioethyl thiazole as a light yellow oil.

n-BuLi (1.6 mL, 2.52 mmol, 1.6 M) was added dropwise to a -78°C solution of 2-thioethyl thiazole (0.35 g, 2.4 mmol) in dry Et_2O (8 mL). The solution was stirred for 1 h at -78°C, then SO_2 gas was bubbled over the surface of the solution for 10 min. The solution was warmed to rt, and the solvent removed. The residue taken up in CH_2Cl_2 (8 mL) and NCS (0.34 g, 2.52 mmol) was added. After stirring at rt 2 h, the solution was filtered and the filtrate concentrated. The residue was dissolved in acetone (8 mL) and NH_4OH (5.0 mL) was added. After 5 min, the acetone was removed in vacuo and the aqueous extracted with EtOAc, dried ($MgSO_4$) and concentrated. The crude material was purified by flash chromatography using 35% EtOAc/hexane to give 0.29 g (53%) of 2-ethylthio-5-thiazole sulfonamide as a light brown solid.

mp 95 - 96°C
^{1}H NMR $CDCl_3$:
7.96(s, 1H), 7.09 (brs, 2H), 3.3 (q, 2H, J = 7.2 Hz), 1.4 (t, 3 H, J = 7.2Hz)
^{13}C NMR $CDCl_3$:
172.0, 145.5, 140.2, 28.9, 14.6
Mass Spect.:

CI - 224 (M^+)
High Res.:
Calcd. $C_5H_8N_2O_2S_3$ 223.9749 (M^+)
Found 223.9766
Elemental Analysis:
Calcd. C 26.77, H 3.59, N 12.49
Found C 27.02, H 3.47, N 12.53

EXAMPLE 31:
2-Ethylsulfonyl-5-thiazole sulfonamide

A solution of Oxone (0.72 g, 1.17 mmol) in water (11 mL) was added dropwise to a solution of 2-thioethyl-5-thiazole sulfonamide (0.15 g, 0.78 mmol) in MeOH (11 mL) at rt. The solution was stirred at rt for 16 h. The solution was cooled to 0°C and saturated $NaHCO_3$ was added dropwise until the solution became basic. The solids were filtered off and washed with MeOH and EtOAc. The filtrate was evaporated, the residue taken up in a minimum volume of water and extracted with EtOAc. The combined extracts were dried (Na_2SO_4), concentrated and purified by flash chromatography using 40% EtOAc/hexane to give 0.15 g of 2-ethylsulfonyl-5-thiazole sulfonamide as a white solid.

mp 129 - 130°C
^{1}H NMR $(CH_3)_2CO$:
8.43(s, 1H), 7.47 (brs, 2H), 3.59 (q, 2H, J = 7.2 Hz), 1.35 (t, 3H, J = 7.2Hz)
^{13}C NMR $(CH_3)_2CO$:
169.4, 148.6, 146.9, 49.8, 7.3
Elemental Analysis:
Calcd. C 23.43, H 3.15, N 10.93
Found C 23.64, H 3.03, N 10.92

EXAMPLE 32:
2-(1-Ketocyclopropyl)-5-thiazole sulfonamide

n-BuLi (26.7mL, 42.8 mmol, 1.6 M) was added dropwise to a -78°C solution of 2-bromothiazole (6.7 g, 40.8 mmol) in dry Et_2O (80 mL). After stirring at -78°C for 1 h, cyclopropanal (32 mL, 42.8 mmol) was added and

the solution stirred 30 min. The reaction was quenched with water, the layers separated and the aqueous extracted with EtOAc. The combined extracts were dried ($MgSO_4$), and condensed. The crude material was purified by flash chromatography using 40% EtOAc/hexane to give 5.98 g (95%) of 2-(1-hydroxy-1-cyclopropylmethyl)thiazole as a yellow oil.

TBDMSCl (3.5 g, 23.2 mmol) and DBU (3.5 mL, 23.2 mmol) were added to a solution of 2-(1-hydroxy-1-cyclopropylmethyl)thiazole (3.0 g, 19.4 mmol) in dry THF (40 mL). The mixture was stirred at rt for 16 h, then quenched with water and the layers separated. The aqueous portion was extracted with EtOAc, the combined extracts dried ($Mg SO_4$) and concentrated. The material was purified by flash chromatography using 5% EtOAc/hexane to give 4.97 g (95%) of 2-(1-t-butyldimethylsiloxy-1-cyclopropylmethyl)thiazole as a colorless oil.

n-BuLi (1.22 mL, 1.95 mmol, 1.6 M) was added dropwise to a -78°C solution of 2-(1-t-butyldimethylsiloxy-1-cyclopropylmethyl)thiazole (0.5 g, 1.86 mmol) in dry THF (18 mL). The solution was stirred for 1 h at -78°C, then SO_2 gas was bubbled over the surface of the solution for 10 min. The solution was warmed to rt, then the solvent was removed and the residue taken up in CH_2Cl_2 (18 mL) and NCS (0.26 g, 1.95 mmol) was added. After stirring at rt for 2 h, the solution was filtered and the filtrate concentrated. The residue was dissolved in acetone (10 mL) and NH_4OH (3.7 mL) was added. After 20 min., the acetone was removed in vacuo and the aqueous extracted with EtOAc, dried ($MgSO_4$) and concentrated. The crude material was dissolved in THF (10 mL) and TBAF (2.8 mL, 1.0 M) was added. After 30 min. the reaction was quenched with water and the layers separated. The aqueous portion was extracted with EtOAc, the combined extracts dried ($MgSO_4$), concentrated and purified by flash chromatography using 60% EtOAc/hexane to give 0.33 g (76%) of 2-(1-hydroxy-1-cyclopropylmethyl)-5-thiazole sulfonamide.

Jones' reagent (0.63 mL, 1.69 mmol, 2.67 M) was added dropwise to a 0°C solution of 2-(1-hydroxy-1-cyclopropylmethyl)-5-thiazole sulfonamide (0.33 g, 1.4 mmol) in acetone (5 mL). The ice bath was removed and the solution stirred for 30 min. The reaction was quenched with a few drops of isopropanol and the acetone removed in vacuo. The residue was taken up in water and extracted with EtOAc. The combined extracts were dried ($MgSO_4$), concentrated and purified by flash chromatography using 30% EtOAc/hexane to give 0.23 g (72%) of 2-(1-ketocyclopropyl)-5-thiazole sulfonamide as a white solid.

mp 148 -149°C

^{1}H NMR $(CD_3)_2CO$:

8.38 (s, 1H), 7.37 (brs, 2H), 3.19 (m, 1H), 1.21 (m, 4H)

^{13}C NMR $(CD_3)_2CO$:

194.0, 170.7, 148.2, 146.8, 14.5, 13.3

Mass Spect.:

High Res.:

Calcd. $C_7H_8N_2O_3S_2$ 231.9976 (M^+)

Found 231.9954

Elemental Analysis:

Calcd. C 36.20, H 3.47, N 12.06

Found C 35.89, H 3.34, N 11.97

EXAMPLE 33:
2-(4-(N,N-dimethyl)aminobutanoyl)-5-thiazole sulfonamide

TMSCl (1.72 mmol, 0.22 mL) was added to a solution of NaI (1.72 mmol, 0.26 g) and 2-(1-ketocyclopropyl)-5-thiazole sulfonamide (0.86 mmol, 0.2 g) in acetonitrile (2 mL). After stirring at rt for two hours, the reaction was still incomplete. The reaction was stirred overnight, NaI (0.26 g) and TMSCl (0.22 mL) were added. Reaction was completed after two hours. Saturated Na_2SO_3 was added and the mixture extracted with ethyl acetate (4x). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated. The residue was subjected to flash chromatography (50% ethyl acetate/hexane) to afford 0.15 g (48%) of 2-(1-hydroxy-4-iodobutyl)-5-thiazole sulfonamide.

TBSOTf (2.53 mmol, 0.58 mL), and pyridine (2.53 mmol, 0.2 mL) were precomplexed in THF (2 mL), then added to a solution of 2-(1-hydroxy-4-iodobutyl)-5- sulfonamide (1.2, 0.43 g). The reaction was stirred at rt for two hours. The reaction was quenched with water and extracted with ethyl acetate, dried (MgSO4), filtered and concentrated. The residue was subjected flash chromatography (25% ethyl acetate/hexane) to afford 0.37 g (64%) of 2-(1-t-butyldimethylsiloxy-4-iodobutyl)-5-thiazole sulfonamide.

Dimethylamine was bubbled through a solution of 2-(1-t-butyldimethylsiloxy-4-iodobutyl)-5-thiazole sulfonamide (0.78 mmol, 0.37g) in THF(8 mL) at 0°C. After 30 minutes the solvent was removed

and the residue taken up in THF and TBAF (1.17 mmol) added. The reaction was stirred at rt for 2 hours. The reaction was concentrated and the residue subjected to flash chromatography (5% MeOH/NH_3/$CHCl_3$) to afford 0.16 g (72%) of 2-(1-hydroxy-4-(N,N-dimethylamino)butyl)-5-thiazole sulfonamide.

A mixture of 2-(1-hydroxy-4-(N,N-dimethylamino)butyl)-5-thiazole sulfonamide (0.35 mmol, 0.098 g) and MnO_2 (5.27 mmol, 0.46 g) in THF was stirred at rt overnight. The mixture was filtered through celite and the solvent removed. The residue was subjected to flash chromatography (10% MeOH/NH_3/$CHCl_3$) to afford 34.4 mg (35%) of 2-(1-keto-4-(N,N-dimethylamino)butyl)-5-thiazole sulfonamide.

2-(4-(N,N-dimethylamino)butanoyl)-5-thiazole sulfonamide (34.4 mg) was stirred with 4 mL of an ethereal solution of HCl. After 2 hours the solvent was removed and the solid left under vacuum.

mp 202 -203°C (decomposed)

^{1}H NMR $(CD_3)_2SO$:

8.43 (s, 1H), 8.21 (brs, 2H), 3.24 (t, 2H, J= 7.9 Hz), 3.12 (m, 2H), 2.78 (s, 6H), 2.0 (m, 2H)

Elemental Analysis:

Calcd. C 34.44, H 5.14, N 13.39

Found C 34.05, H 5.02, N 12.98

EXAMPLE 34:

2-(1-Butoxy)-5-thiazole sulfonamide

A suspension of NaH (6.7 mmol, 0.27 g, 60 % dispersion) in dry DMF was stirred with butanol (6.09 mmol, 0.55 mL) under argon until evolution of hydrogen ceased. 2-Bromothiazole (6.09 mmol, 0.55 mL) was added and after 15 minutes the mixture was heated to reflux. After 48 hours the reaction was quenched with water and extracted with ethyl acetate (4x). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated. The residue was subjected to flash chromatography (hexane followed with 1% ethyl acetate) to afford 0.35 g (37%) of 2-(1-butoxy)thiazole as an amber oil.

n-BuLi (1.79 mmol, 1.1 mL, 1.6 M) was added dropwise to a -78°C solution of 2-(1-butoxy)thiazole (0.27 g, 1.7 mmol) in dry THF (15 mL). The solution was stirred for 1 h at -78°C, then SO_2 gas was bubbled over

the surface of the solution for 10 min. The solution was warmed to rt, then the solvent was removed and the residue taken up in CH_2Cl_2 (15 mL) and NCS (0.24 g, 1.79 mmol) was added. After stirring at rt for 30 minutes, the solution was filtered and the filtrate concentrated. The residue was dissolved in acetone (15 mL) and NH_4OH (3.4 mL) was added. After 5 min, the acetone was removed in vacuo and the aqueous extracted with EtOAc, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography using 25% EtOAc/hexane to give 0.26 g (65%) of 2-(1-butoxy)-5-thiazole sulfonamide.

^{1}H NMR $(CD_3)_2CO$:

7.54 (s, 1H), 6.98 (brs, 2H), 4.48 (t, 2H, J= 6.5 Hz), 1.74-1.83 (m, 2H), 1.42-1.49 (m, 2H), 0.95 (t, 3H, J= 7.3 Hz)

^{13}C NMR $(CD_3)_2SO$:

177.91, 141.17, 133.00, 73.37, 31.29, 19.48, 13.83

Mass Spect.:

EI - 236 (M^+)

High Res.:

Calcd. 236.02893

Found 236.0287

Elemental Analysis:

Calcd. C 35.58, H 5.12, N 11.85

Found C 35.63, H 5.12, N 11.81

EXAMPLE 35:
2-(1-Hexynyl)-5-thiazole sulfonamide

2-Bromothiazole (6.09 mmol,1.0 g) was added to 40 mL of acetonitrile. CuI (1.52 mmol, 0.29 g), triethylamine (7.31 mmol, 1.01 mL) and bistriphenylphosphine palladium chloride (0.3 mmol, 0.21 g) were added and the solution degassed. Hexyne (6.09 mmol, 0.7 mL) was added and the mixture heated at refluxed overnight. Water was added followed by NaCl and ether. The layers were separated and the aqueous layer extracted with ether (4x). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated. The residue was subjected to flash chromatography (10% ethyl acetate/hexane) to afford 0.36 g (36%) of 2-(1-hexynyl)thiazole.

n-BuLi (2.1 mmol, 1.3 mL, 1.6 M) was added dropwise to a -78°C solution of 2-(1-hexynyl)thiazole (0.33 g, 2.0 mmol) in dry THF (20 mL). The solution was stirred for 1 h at -78°C, then SO_2 gas was bubbled over the surface of the solution for 10 min. The solution was warmed to rt, then the solvent was removed and the residue taken up in CH_2Cl_2 (20 mL) and NCS (0.28 g, 2.10 mmol) was added. After stirring at rt for 1 hour, the solution was filtered and the filtrate concentrated. The residue was dissolved in acetone (20 mL) and NH_4OH (4 mL) was added. After 10 min., the acetone was removed in vacuo and the aqueous extracted with EtOAc, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography using 30% EtOAc/hexane to give 0.27 g (56%) of 2-(1-hexynyl)-5-thiazole sulfonamide.

^{1}H NMR $(CD_3)_2CO$:

8.1 (s, 1H), 7.25 (brs, 2H), 2.55 (t, 2H, J= 7 Hz), 1.61 (m, 2H), 1.48 (m, 2H), 0.93 (t, 3H, J= 7.2 Hz)

^{13}C NMR $(CD_3)_2SO$:

153.20, 145.74, 142.27, 100.04, 74.09, 30.50, 22.51, 19.38, 13.70

Mass Spect.:

EI - 244 (M^+)

High Res.:

Calcd. 244.0340

Found 244.0352

Elemental Analysis:

Calcd. C 44.24, H 4.95, N 11.47

Found C 44.30, H 4.92, N 11.38

EXAMPLE 36:
2-(1-Hexyl)-5-thiazole sulfonamide

2-(1-hexynyl)-5-thiazole sulfonamide (0.04 g, 0.16 mmol) was dissolved in 5 mL of methanol. 0.01 g of palladium/carbon was added and the solution purged three times with hydrogen. The reaction was left under 30 psi of hydrogen for 48 hours. The mixture was filtered through celite and the filtrate concentrated. The residue was purified on the chromatatron (eluted with 5:1.5:3.5 CH_2Cl_2/Et_2O, hexane) to afford 32 mg (80%) of 2-hexyl-5-thiazole sulfonamide.

^{1}H NMR $(CD_3)_2CO$:

7.98 (s, 1H), 7.07 (brs, 2H), 3.03 (t, 2H, J= 7.7 Hz), 1.78 (m, 2H), 1.32 (m, 4H), 0.87 (t, 3H, J= 6.8 Hz)

^{13}C NMR $(CD_3)_2SO$:

176.92, 145.28, 141.24, 33.98, 32.08, 30.31, 29.22, 23.09, 14.23

Elemental Analysis:

Calcd. C 43.52, H 6.49, N 11.28

Found C 43.62, H 6.68, N 11.18

EXAMPLE 37

2-Phenyl-5-thiazole sulfonamide

2-Bromothiazole (1.2 mmol, 0.11 mL) and phenylboric acid (1.2 mmol, 0.146 g) were added to a solution of potassium carbonate (2M, 1.2 mL) and ethanol (0.6 mL) in deoxygenated toluene (12 mL). The resulting mixture was degassed for 30 minutes, then tetrakistriphenylphosphine palladium (0.036 mmol, 0.042 g) was added and the solution heated at reflux for 48 hours. The solids were removed by filtration and the solution extracted with toluene (5x), dried ($MgSO_4$), filtered and concentrated. The residue was subjected to flash chromatography (hexane followed with 5% ethyl acetate/hexane and then 10% ethyl acetate/hexane) to afford 0.13 g (69%) of 2-phenylthiazole.

n-BuLi (0.86 mmol, 0.54 mL, 1.6 M) was added dropwise to a -78°C solution of 2-phenylthiazole (0.13 g, 0.82 mmol) in dry THF (8 mL). The solution was stirred for 1 h at -78°C, then SO_2 gas was bubbled over the surface of the solution for 10 min. The solution was warmed to rt, then the solvent was removed and the residue taken up in CH_2Cl_2 (8 mL) and NCS (0.11 g, 0.86 mmol) was added. After stirring at rt for 2 hour, the solution was filtered and the filtrate concentrated. The residue was dissolved in acetone (1 mL) and NH_4OH (1.6 mL) was added. After 10 min, the acetone was removed in vacuo and the aqueous extracted with EtOAc, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography using 30% EtOAc/hexane to give 0.093 g (47%) of 2-phenyl-5-thiazole sulfonamide.

m.p. 209-210°C

^{1}H NMR $(CD_3)_2CO$:

8.20 (s, 1H), 8.03 (m, 2H), 7.55 (m, 3H), 7.21 (brs, 2H)

^{13}C NMR $(CD_3)_2SO$:

172.63, 146.50, 141.76, 133.36, 132.20, 130.11, 127.48

Mass Spect.:

EI - 240 (M^+)

High Res.:

Calcd. 240.0027

Found 240.0025

Elemental Analysis:

Calcd. C 44.98, H 3.36, N 11.66

Found C 45.12, H 3.35, N 11.58

EXAMPLE 38:

2-(2-(methoxymethoxy)ethanoyl-5-thiazole sulfonamide

n-BuLi (9.96 mmol, 6.2 mL, 1.6 M) was added dropwise to a -78°C solution of diisopropylamine (1.4 mL, 9.96 mmol) in dry THF (20 mL). The solution was stirred for 10 min. at 0°C, then tributyltinhydride (9.96 mmol, 2.68 mL) was added and the solution stirred for 15 min. The solution was cannulated into a 0°C solution of paraformaldehyde (9.96 mmol, 0.3 g) and the solution stirred at rt for 3 hours. The reaction was quenched with NH_4Cl and extracted with pentane (4x), dried ($MgSO_4$), and concentrated. The crude material was dissolved in CH_2Cl_2 (40 mL), dimethylaniline (14.9 mmol, 1.9 mL) was added and the solution cooled to 0°C. Chloromethylmethylether (14.9 mmol, 1.13 mL) was added and the reaction stirred for 2 hours. The reaction was diluted with pentane and then washed with cold 0.5 M HCl, water, saturated $NaHCO_3$ and dried (Na_2SO_4). Flash chromatography (25% CH_2Cl_2/hexane) affords 1.49 g (41%) of (methoxymethoxymethyl)tributyl tin.

n-BuLi (2.87 mmol, 1.8 mL, 1.6 M) was added dropwise to a -78°C solution of (methoxymethoxymethyl)tributyl tin (1.05 g, 2.87 mmol) in dry THF (10 mL). After stirring for 30 minutes a solution of 2-formylthiazole (2.73 mmol, 0.31 g) in THF (2mL) was added and the solution stirred overnight. The reaction was diluted with water and extracted with ethyl acetate, dried ($MgSO_4$), filtered and concentrated. The residue was subjected to flash chromatography (45% ethyl acetate/hexane) to afford 0.18 g (34%) of 2-(1-hydroxy-2-(methoxymethoxy)ethyl)thiazole.

A mixture of 2-(1-hydroxy-2-(methoxymethoxy)ethyl)thiazole (0.93 mmol, 0.18 g), TBSCl (1.1 mmol, 0.17 g) and DBU (1.1 mmol, 0.16 mL) in THF (1 mL) was stirred at rt overnight. The reaction was diluted with water and extracted with ethyl ether, dried ($MgSO_4$), filtered and concentrated. The residue was subjected to flash chromatography (10% ethyl acetate/hexane) to afford 0.20 g (70%) of 2-(1-(t-butyldimethylsiloxy)-2-(methoxymethoxy)ethyl)thiazole.

n-BuLi (0.68 mmol, 0.42mL, 1.6 M) was added dropwise to a -78°C solution of 2-(1-(t-butyldimethylsiloxy)-2-(methoxymethoxy)ethyl)thiazole (0.20g, 0.65 mmol) in dry THF (6 mL). The solution was stirred for 1 h at -78°C, then SO_2 gas was bubbled over the surface of the solution for 10 min. The solution was warmed to rt, then the solvent was removed and the residue taken up in CH_2Cl_2 (6 mL) and NCS (0.42 g, 0.68 mmol) was added. After stirring at rt for 2 hour, the solution was filtered and the filtrate concentrated. The residue was dissolved in acetone (2 mL) and NH_4OH (1.3 mL) was added. After 15 min., the acetone was removed in vacuo and the aqueous extracted with EtOAc, dried ($MgSO_4$) and concentrated. The residue was taken up in THF (6 mL) and treated with TBAF (0.78 mmol, 0.78 mL) for 30 minutes at rt. Water was added and the solution extracted with ethyl acetate, dried ($MgSO_4$), filtered and concentrated. The residue was subjected to flash chromatography (70% ethyl acetate/hexane) to afford 86 mg (49%) of 2-(1-hydroxy-2-(methoxymethoxy)ethyl)-5-thiazole sulfonamide.

Jones' reagent (0.14 mL, 0.39 mmol, 2.67 M) was added dropwise to a 0°C solution of 2-(1-hydroxy-2-(methoxymethoxy)ethyl)-5-thiazole sulfonamide (0.086 g, 0.32 mmol) in acetone (1 mL). The ice bath was removed and the solution stirred for 15 min. The reaction was incomplete an additional 0.07 mL of Jones' reagent was added and the reaction stirred for 15 more minutes. The reaction was quenched with a few drops of isopropanol and the acetone removed in vacuo. The residue was taken up in water and extracted with EtOAc. The combined extracts were dried ($MgSO_4$), concentrated and purified by flash chromatography using 55% EtOAc/hexane to give 4.8 mg (5.3%) of 2-(2-(methoxymethoxy)-ethanoyl)-5-thiazole sulfonamide.

^{1}H NMR $(CD_3)_2CO$:

8.35 (s, 1H), 7.39 (brs, 2H), 5.03 (s, 2H), 4.72 (s, 2H), 3.35 (s, 3H)

^{13}C NMR $(CD_3)_2SO$:

190.19, 168.57, 146.82, 146.69, 97.30, 97.23, 69.68, 69.61, 55.75, 55.64

Mass Spect.:

EI - 267 (MH^+)

High Res.:

Calcd. 267.0119 (MH^+)

Found 267.0119

EXAMPLE 39:

2-(N-t-butylsulfamyl)-5-thiazole sulfonamide

To a solution of 2-N-t-butylthiazole sulfonamide (0.5g, 2.3mol) in 23mL of THF at -78°C was added n-butyllithium (1.6M, 2.9mL, 4.6mmol). The reaction was stirred under argon at -78°C for 60 min. An excess of SO_2 was bubbled through the reaction. The reaction was slowly warmed to rt and then concentrated under reduced pressure. The crude product was added to 35mL of dichloromethane. N-chlorosuccinamide (0.34g, 2.53mmol) was added and the reaction stirred at rt for 60 min. The mixture was filtered and the filtrate collected and concentrated under reduced pressure. To the crude product in 30mL of acetone was added 2ml of concentrated ammonium hydroxide in 10mL of acetone. The reaction was acidified with 1N HCl and then extracted with ethyl acetate. The organic phase was washed with water and then brine. The solvent was removed under reduced pressure and the product subjected to flash chromatography (1:1 hexane/ethyl acetate). 0.27g (0.9mmol, 39%) of 2-(N-t-butylsulfamyl)-5-thiazole sulfonamide (white crystals) was recovered.

^{1}H NMR $(CD_3)_2CO$:

8.29 (s, 1H), 7.35 (bs, 3H), 1.32 (s, 9H)

^{13}C NMR $(CD_3)_2CO$:

173.3, 146.7, 146.0, 56.1, 30.2

Mass Spect.:

EI - 300 (MH^+)

High Res.:

Calcd. 283.9833 ($M-CH_3$)

Found 283.9833 ($M-CH_3$)

Elemental Analysis:

Calcd. C 28.09, H 4.35, N 14.05

Found C 28.17, H 4.12, N 14.10

EXAMPLE 40:
2-(N-Methyl-N-(dimethylamino)ethyl)sulfamyl-5-thiazole sulfonamide

To a solution of 2-bromothiazole (5.0g, 0.03mol) in 122mL of ethyl ether at -78°C was added n-butyllithium (1.6M, 19.1mL, 0.03mmol). The reaction was stirred under argon at -78°C for 60 min. An excess of SO_2 was bubbled through the reaction. The reaction was slowly warmed to rt and then concentrated under reduced pressure. The crude product was added to 125mL of dichloromethane. N-chlorosuccinamide (4.5g, 0.033mmol) was added and the reaction stirred at rt for 30 min. The mixture was filtered and the filtrate collected and concentrated under reduced pressure. To the crude product in 22mL of THF was added trimethylethylene diamine (5.5mL , 0.15mmol). The reaction was stirred at rt for 15 min. and then quenched with water. The organic phase was washed with water (3X) followed by brine. The solvent was removed under reduced pressure and the product subjected to flash chromatography (10:1 chloroform/methanol). 1.1g of 2-(N-methyl-N-(dimethylamino)ethyl)sulfamyl thiazole was recovered.

To a solution of 2-(N-methyl-N-(dimethylamino)ethyl)sulfamyl thiazole (1.1g, 4.42mmol) in 44mL of THF at -78°C was added n-butyllithium (1.6M, 2.8mL, 4.42mmol). The reaction was stirred under argon at -78°C for 60 min. An excess of SO_2 was bubbled through the reaction. The reaction was slowly warmed to rt and then concentrated under reduced pressure. The crude product was added to 44mL of dichloromethane. N-chlorosuccinamide (0.65g, 4.86mmol) was added and the reaction stirred at rt for 2h. An additional 0.65g of N-chlorosuccinamide was added and the reaction stirred at rt for another 30min.The mixture was filtered and the filtrate collected and concentrated under reduced pressure. To the crude product in 50mL of acetone was added 5mL of concentrated ammonium hydroxide in 10mL of acetone. Upon completion the reaction was diluted with water and extracted with ethyl acetate. The organic phase was washed with water (3X) followed by brine. The solvent was removed under reduced pressure and the product subjected to flash chromatography (4:1 chloroform/ methanol). 0.25g (0.76mmol, 17%) of 2-(N-methyl-N-(dimethylamino)ethyl)sulfonyl-5-thiazole sulfonamide (tan crystals) was recovered.

^{1}H NMR $(CD_3)_2CO$:

8.32(s, 1H), 7.40 (bs, 2H), 3.41 (t, J= 6.2 Hz, 2H), 3.08 (s, 3H), 2.45 (t, J= 6.2 Hz, 2H), 2.10 (s, 6H)

^{13}C NMR $(CD_3)_2CO$:

169.4, 146.4, 146.3, 57.5, 49.3, 45.4, 36.1

Mass Spect.:

CI - 329 (MH^+)

High Res.:

Calcd. 329.0412

Found 329.0424

Elemental Analysis:

Calcd. C 29.27, H 4.88, N 17.07

Found C 29.42, H 4.73, N 16.95

EXAMPLE 41:
4-Methyl-1-(2-sulfamylthiazolyl)sulfonyl)piperazine

To a solution of 2-thiazole sulfonylchloride (4.0g, 0.022mol) in 80mL of THF at rt was added N-methyl piperazine (2.9 mL, 0.026mol) in 10mL of THF. The reaction was stirred for 10 min. and then diluted with ethyl acetate. The reaction was washed with water (3X) followed by brine. The solvent was removed under reduced pressure and the product subjected to flash chromatography (20:1 chloroform/methanol). 0.92g of 2-thiazoylsulfonyl piperazine was recovered.

To a solution of 2-thiazoylsulfonyl piperazine (0.92g, 3.7mmol) in 37mL of THF at -78°C was added n-butyllithium (2.3mL, 3.7mmol). The solution was stirred under argon at -78°C for 60 min. An excess of SO_2 was bubbled through the reaction. The reaction was slowly warmed to rt and then concentrated under reduced pressure. The crude product was added to 40mL of dichloromethane. N-chlorosuccinamide (0.54g, 4.1mmol) was added and the reaction stirred at rt for 1.5h. The mixture was filtered and the filtrate collected and concentrated under reduced pressure. To the crude product in 40mL of acetone was added 3mL of concentrated ammonium hyroxide in 10mL of acetone. Upon completion the reaction was diluted with water and extracted with ethyl acetate. The organic phase was washed with water (3X) followed by brine. The solvent was removed under reduced pressure and the product subjected to flash

chromatography (4:1 chloroform/methanol). 40mg (0.12mmol, 3.3%) of 4-methyl-1-(2-(5-sulfamylthiazoyl)sulfonyl)piperazine (tan crystals) was recovered.

^{1}H NMR $(CD_3)_2CO$:

8.39 (s, 1H), 7.42 (bs, 2H), 3.32 (t, J= 5 Hz, 4H), 2.45 (t, J= 5 Hz, 4H), 2.23 (s, 3H)

^{13}C NMR $(CD_3)_2CO$:

167.43, 147.26, 146.70, 54.67, 47.24, 45.87

Mass Spect.:

CI - 327 (MH^+)

High Res.:

Calcd. 327.0255

Found 327.0233

Elemental Analysis:

Calcd. C 29.45, H 4.29, N 17.18

Found C 29.53, H 4.17, N 17.14

The compounds of the invention were assayed for biological activity as follows:

1. Carbonic anhydrase activity was assayed according to the micromethod of Maren (*J. Pharmacol. Exptl. Therap.*, 130, 26-29, 1960). All solutions and reagents were maintained at 0-4°C. The final assay mixture contained 16 mM phenol red, added enzyme and 62.5 mM sodium carbonate/bicarbonate. Its volume was kept constant at 0.8mL. The time required for the added enzyme to lower the pH of CO2-saturated carbonate/bicarbonate buffer from pH 9.9 to 6.8 was measured using the color change of phenol red as endpoint. T1 is the time recorded for the reaction containing no enzyme. T2 is the time recorded for the reaction containing pure CA11 enzyme from human erythrocyte, or an unknown amount in a sample. Enzyme activities (unit) were calculated using the formula:

$$\text{Unit/ug} = (T_1 - T_2)(T_2 * \text{ug protein used in assay})$$

IC_{50} of a carbonic anhydrase inhibitor is the concentration that lowers the enzyme activity to half.

The results of this assay are reported in Table 1, below.

Table I

Name of structure	IC_{50} in nM	Cysteine reactivity
2-Thiazole sulfonamide	61 nM	N.R.
5-Benzoyl-2-thiazole sulfonamide	5 nM	reactive
5-Phenylsulfonyl-2-thiazole sulfonamide	6 nM	reactive
5-(Phenylthio)-2-thiazole sulfonamide	2.7 nM	0.005
5-Chloro-2-thiazole sulfonamide	5.9 nM	0.00002
5-(Ethylthio)-2-thiazole sulfonamide	4.2 nM	0.000024
5-(2-Hydroxyethylthio)-2-thiazole sulfonamide	6.6 nM	–
4-Methyl-2-thiazole sulfonamide	120 nM	0.00005
4-Carboethoxy-2-thiazole sulfonamide	77 nM	<0.000005
5-(4-Acetoxybutanoyl)-2-thiazole sulfonamide	8.4 nM	reactive
5-Ethylsufinyl-2-thiazole sulfonamide	11.4 nM	reactive
5-Bromo-2-thiazole sulfonamide	7.8 nM	–
5-Methyl-4-phenyl-2-thiazole sulfonamide	84 nM	N.R.
2-Sulfamyl-4,5,6,7-tetrahydrobenzothiazole	15 nM	–
5-(1-Hexynyl)-2-thiazole sulfonamide	5.6 nM	0.00019
5-Phenyl-2-thiazole sulfonamide	6 nM	–
4-Phenyl-2-thiazole sulfonamide	20 nM	–
5-(2-Carbomethoxyethylthio)-2-thiazole sulfonamide	9.1nM	–
5-Benzyloxycarbonyl-2-sulfamyl-4,5,6,7-tetrahydrothiazole[5,4-c]pyridine	11 nM	–
5-Chloro-4-(4-methoxyphenyl)-2-thiazole sulfonamide	30 nM	–
5-Benzyl-2-thiazole sulfonamide	9.3 nM	–
4-(4-Methoxyphenyl)-2-thiazole sulfonamide	33 nM	–

2-(1-Hydroxyhexyl)-5-thiazole sulfonamide	10 nM	–
2-(Ethylthio)-5-thiazole sulfonamide	6.3 nM	<0.0000024
2-(Ethylsulfonyl)-5-thiazole sulfonamide	6.7 nM	reactive
2-(Phenylsulfonyl)-5-thiazole sulfonamide	5.5 nM	reactive
2-Hexanoyl-5-thiazole sulfonamide	3.5 nM	0.00007
2-Phenylthio-5-thiazole sulfonamide	5.5 nM	N.R.
2-Cyclopropylcarbonyl-5-thiazole sulfonamide	3.5 nM	<0.000024
2-(N-t-butylsulfamyl)-5-thiazole sulfonamide	5.3 nM	–
2-(N-Methyl-N-(dimethylamino)-ethyl)sulfamyl-5-thiazole sulfonamide	14.5 nM	reactive
2-(1-Keto-2-methoxymethoxymethyl)-5-thiazole sulfonamide	10.3 nM	–
1-(2-(-Sulfamylthiazolyl)sulfonyl)-4-methyl-piperazine	9.3 nM	reactive
(2-(5-Sulfamylthiazolyl))(phenyl)-sulfoxide	12.7 nM	reactive
2-(4-(N,N-Dimethylamino)butanoyl)-5-thiazole sulfonamide hydrochloride	26 nM	–
2-(1-Butoxy)-5-thiazole sulfonamide	16 nM	<0.00005
2-(1-Hexynyl)-5-thiazole sulfonamide	7.7 nM	0.001
2-Phenyl-5-thiazole sulfonamide	20 nM	–
2-Hexyl-5-thiazole sulfonamide	20.6 nM	–

2. Cysteine reactivity was measured by the following probe assay procedure. Three stock solutions of: A) the CAI compound to be tested in 50 nM phosphate buffer; B) cysteine (10nM) in 50 mM phosphate buffer at pH 7.4; and C) phosphate buffer (50 mM) at pH 7.4, were prepared. Each solution was deoxygenated by bubbling with N_2 for 10-15 min.

Reaction mixtures were prepared in triplicate by mixing equal volumes (1 mL) of two stock solutions as follows:

I) A + B at 4°C

II) A + B at RT
III) A + C at RT

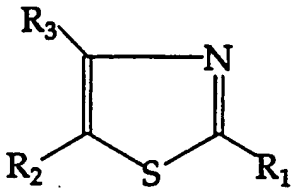
Hydrolytic or other chemical reactivity was detected by comparison of solutions I and II. Cysteine related reactions were detected by comparison of solutions II and III. All samples were assayed using HPLC under constant conditions and over a short period of time to minimize experimental variations in peak heights not related to CAI concentration differences. Each of the three solutions were assayed in sequence to give three sets of experimental values: Ia, IIa, IIIa, Ib, IIb, IIIb, Ic, IIc, IIIc and each set was compared separately. Mean and standard deviations of the three sets were recorded.

While particular embodiments of the invention have been described it will be understood of course that the invention is not limited thereto since many obvious modifications can be made and it is intended to include within this invention any such modifications as fall within the scope of the appended claims.

CLAIMS

Having now described the invention, what is claimed is:

1. A compound having the formula:



wherein R_1 is: $-SO_2NH_2$; $-S(O)_nR_4$; $-C(O)R_4$; $-OR_4$; phenyl, heteroaryl, aralkyl, heteroaralkyl, aralkenyl or heteroaralkenyl having from 5 to 6 atoms in the aryl moiety and 1 to 2 carbon atoms in the alkyl or 2 carbon atoms in the alkenyl moiety; alkyl having from 1 to 8 carbon atoms, or alkenyl or alkynyl having from 2 to 8 carbon atoms which can optionally be substituted with one or more hydroxy or carboxy groups

wherein R_4 is: hydrogen; alkyl having from 1 to 6 carbon atoms or alkenyl or alkynyl having from 2 to 6 carbon atoms optionally substituted by dimethylamine; alicyclic having from 3 to 6 carbon atoms; carbalkoxyalkyl having 1 to 4 carbon atoms in the carbonyl moiety and from 1 to 6 carbon atoms in the alkoxy moiety; phenyl; $CH_3OCH_2OCH_2$; lower dialkylamino optionally further substituted by dimethylamine; or saturated nitrogen-containing heterocycles containing from 5 to 7 atoms optionally substituted with alkyl having from 1 to 3 carbon atoms and n is 0, 1 or 2;

R_2 is: $-SO_2NH_2$; $-S(O)_nR_4$; $-C(O)R_4$; $-OR_4$; bromo; chloro; aryl or heteroaryl having from 5 to 6 atoms; alkyl having from 1 to 8 carbon atoms, or alkenyl or alkynyl having from 2 to 8 carbon atoms which can optionally be substituted with one or more hydroxy groups wherein R_4 and n are as defined above;

R_3 is: hydrogen; alkyl of 1 to 6 carbon atoms; carboxy; lower carboxy alkyl; or phenyl optionally mono- or di-substituted with lower alkoxy, fluoro, chloro, bromo or alkyl of 1 to 3 carbon atoms; or R_2 and R_3 taken together form a ring fused with the 4-5 positions of the thiazole ring and are chosen from the group consisting of tetrahydrobenzene,

tetrahydropyridine and thiopyran and can optionally be substituted by carboxylic acid, lower alkyl or benzyl esters of carboxylic acid, lower alkyl, or halogen;

provided that at least one of R_1 and R_2 must represent the sulfonamide moiety, $-SO_2NH_2$.

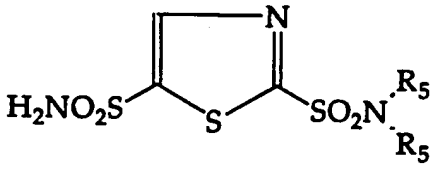
2. The compound of claim 1 wherein R_1 is primary sulfonamide, R_2 is as defined in claim 1 and R_3 is hydrogen.

3. The compound of claim 1 wherein R_1 is as defined in claim 1, R_2 is primary sulfonamide and R_3 is hydrogen.

4. The compound of claim 1 wherein R_2 and R_3, together, represent the optionally substituted ring fused to the thiazole ring and R_1 is primary sulfonamide.

5. The compound of claim 3 wherein R_1 is $-S(O)_nR_4$, $-C(O)R_4$, benzyl, $-CH=CHR_4$, or $-C\equiv CR_4$ wherein R_4 is chosen from the group consisting of phenyl, a straight or branched carbon chain of up to 6 atoms, and alicycles of 3 to 6 carbon atoms.

6. The compound of claim 1 having the following structure:

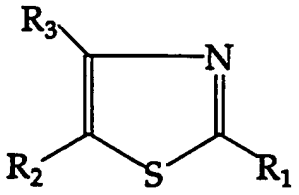


wherein each R_5 independently is chosen from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms; phenyl, lower dialkylamino optionally further substituted by dimethylamine, and saturated nitrogen-containing heterocycles containing from 5 to 7 atoms optionally substituted with alkyl having from 1 to 3 carbon atoms.

7. The compound of claim 1 wherein R_1 is $-SO_2NH_2$ and R2 is chosen from the group consisting of phenylthio, ethylthio, chloro, bromo, 2-hydroxyethylthio, 1-hexynyl, phenyl, benzyl and 2-carbomethoxy-ethylthio, and R_3 is hydrogen.

8. The compound of claim 1 wherein R_2 is $-SO_2NH_2$ and R_1 is chosen from the group consisting of phenylthio, ethylthio, cyclopropylketo, 1-hexynyl, 1-hydroxyhexyl and hexanoyl, and R_3 is hydrogen.

9. A method of treating the elevated intraocular pressure of a patient which comprises administering to said patient an effective amount of a compound having the formula:



wherein R_1 is: $-SO_2NH_2$; $-S(O)_nR_4$; $-C(O)R_4$; $-OR_4$; phenyl, heteroaryl, aralkyl, heteroaralkyl, aralkenyl or heteroaralkenyl having from 5 to 6 atoms in the aryl moiety and 1 to 2 carbon atoms in the alkyl or 2 carbon atoms in the alkenyl moiety; alkyl having from 1 to 8 carbon atoms, or alkenyl or alkynyl having from 2 to 8 carbon atoms which can optionally be substituted with one or more hydroxy or carboxy groups

wherein R_4 is: hydrogen; alkyl having from 1 to 6 carbon atoms or alkenyl or alkynyl having from 2 to 6 carbon atoms; alicyclic having from 3 to 6 carbon atoms; lower carbalkoxyalkyl; phenyl; $CH_3OCH_2OCH_2$; lower dialkylamino optionally further substituted by dimethylamine; or saturated nitrogen-containing heterocycles containing from 5 to 7 atoms optionally substituted with alkyl having from 1 to 3 carbon atoms and n is 0, 1 or 2;

R_2 is: $-SO_2NH_2$; $-S(O)_nR_4$; $-C(O)R_4$; $-OR_4$; hydrogen; bromo; chloro; aryl or heteroaryl having from 5 to 6 atoms; alkyl having from 1 to 8 carbon atoms, or alkenyl or alkynyl having from 2 to 8 carbon atoms which can optionally be substituted with one or more hydroxy groups wherein R_4 and n are as defined above;

R_3 is: hydrogen; alkyl of 1 to 6 carbon atoms; carboxy; carboxy alkyl of 1 to 4 carbon atoms; or phenyl optionally mono- or di-substituted with lower alkoxy, fluoro, chloro, bromo or alkyl of 1 to 3 carbon atoms; or R_2 and R_3 taken together form a ring fused with the 4-5 positions of the thiazole

ring and are chosen from the group consisting of tetrahydrobenzene, tetrahydropyridine and thiopyran and can optionally be substituted by carboxylic acid, lower alkyl or benzyl esters of carboxylic acid, lower alkyl, or halogen;

provided that at least one of R_1 and R_2 must represent the sulfonamide moiety, $-SO_2NH_2$, and pharmaceutically acceptable salts and mixtures thereof.

10. The method of claim 9 which comprises topically administering said compound to the eye.

11. A method of treating the elevated intraocular pressure of glaucoma in a patient which comprises administering to said patient an effective amount of a compound according to claim 9.

12. The method of claim 11 which comprises topically administering to the eye said compound of claim 8.

13. The method of claim 12 which comprises administering a unit it dosage of from 0.001 to 10.0 mg of the compound of claim 8 on a daily basis.

14. A pharmaceutical composition for treating a patient having glaucoma, by topical administration to the eye, which comprises an effective amount of a compound according to claim 1 in a pharmaceutically-acceptable carrier.

15. The composition of claim 14 comprising from 0.01 to 15% of said compound of claim 1.

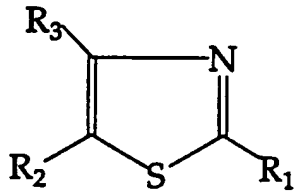
16. A method of inhibiting carbonic anhydrase activity in a patient which comprises administering to said patient an effective amount of a compound according to claim 1.

17. The method of claim 16 which comprises topically administering to the eye said compound of claim 1.

18. The method of claim 17 which comprises administering a unit dosage of from 0.001 to 10.0 mg of the compound of claim 1 on a daily basis.

AMENDED CLAIMS
[received by the International Bureau on 27 July 1995 (27.07.95); original claims 1,5,9 and 13 amended; remaining claims unchanged (5 pages)]

1. A compound having the formula:



wherein R_1 is:

$-SO_2NH_2$; $-S(O)_nR_4$; $-OR_4$; $-C(O)R_6$; phenyl, heteroaryl, aralkyl, heteroaralkyl, aralkenyl or heteroaralkenyl having from 5 to 6 atoms in the aromatic moiety and 1 to 2 carbon atoms in the alkyl or 2 carbon atoms in the alkenyl moiety; alkyl, alkenyl or alkynyl having from 2 to 8 carbon atoms which can optionally be substituted with one or more hydroxy or carboxy groups

wherein R_4 is:

hydrogen; alkyl having from 1 to 6 carbon atoms or alkenyl or alkynyl having from 2 to 6 carbon atoms optionally substituted by dimethylamine; alicyclic having from 3 to 6 carbon atoms; lower carbalkoxyalkyl having 1 to 4 carbon atoms in the carbonyl moiety and from 1 to 6 carbon atoms in the alkoxy moiety; phenyl; $CH_3OCH_2OCH_2$; lower dialkylamino optionally further substituted by dimethylamine; or saturated nitrogen-containing heterocycles containing from 5 to 7 atoms optionally substituted with alkyl having from 1 to 3 carbon atoms

and R_6 is:

alkyl, alkenyl, or alkynyl or alicyclic having from 3 to 6 carbon atoms; lower carbalkoxyalkyl; or $CH_3OCH_2OCH_2$-

and n= 0 - 2

R_2 is:

$-SO_2NH_2$; $-S(O)_nR_4$; $-C(O)R_4$; $-OR_4$; bromo, chloro; aryl or heteroaryl having from 5 to 6 atoms; alkyl having from 1 to 8 carbon atoms, or

alkenyl or alkynyl having from 2 to 8 carbon atoms which can optionally be substituted with one or more hydroxy groups,

wherein R_4, R_5 and n are as defined above;

R_3 is:

hydrogen; alkyl of 1 to 6 carbon atoms; carboxy; lower carboxy alkyl; or phenyl optionally mono- or di-substituted with lower alkoxy, fluoro, chloro, bromo or alkyl of 1 to 3 carbon atoms; or R_2 and R_3 taken together form a ring fused at the 4-5 positions of the thiazole ring and are chosen from the group consisting of tetrahydrobenzene and tetrahydropyridine and can optionally be substituted by carboxylic acid or lower alkyl or benzyl esters of carboxylic acid, lower alkyl, or halogen;

provided that at least one of R_1 and R_2 must represent the sulfonamide moiety, $-SO_2NH_2$ and that R_2 cannot be chloro or bromo when R_3 is methyl, carboxylic acid or esters thereof, or unsubstituted phenyl.

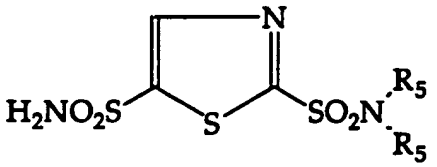
2. The compound of claim 1 wherein R_1 is primary sulfonamide, R_2 is as defined in claim 1 and R_3 is hydrogen.

3. The compound of claim 1 wherein R_1 is as defined in claim 1, R_2 is primary sulfonamide and R_3 is hydrogen.

4. The compound of claim 1 wherein R_2 and R_3, together, represent the optionally substituted ring fused to the thiazole ring and R_1 is primary sulfonamide.

5. The compound of claim 3 wherein R_1 is $-S(O)_nR_4$, $-C(O)R_6$, benzyl, $-CH=CHR_4$, or $-C\equiv CR_4$ wherein R_4 and R_6 are chosen from the group consisting of phenyl, a straight or branched carbon chain of 3 to 6 carbon atoms and alicycles of 3 to 6 carbon atoms.

6. The compound of claim 1 having the following structure:

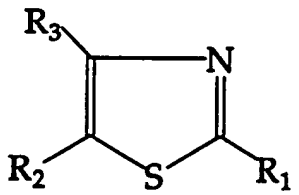


wherein each R_5 independently is chosen from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms; phenyl, lower dialkylamino optionally further substituted by dimethylamine, and saturated nitrogen-containing heterocycles containing from 5 to 7 atoms optionally substituted with alkyl having from 1 to 3 carbon atoms.

7. The compound of claim 1 wherein R_1 is SO_2NH_2 and R_2 is chosen from the group consisting of phenylthio, ethylthio, chloro, bromo, 2-hydroxyethylthio, 1-hexynyl, phenyl, benzyl, and 2-carbomethoxy-ethylthio, and R_3 is hydrogen.

8. The compound of claim 1 wherein R_2 is SO_2NH_2 and R_1 is chosen from the group consisting of phenylthio, ethylthio, cyclopropylketo, 1-hexynyl, 1-hydroxyhexyl and hexanoyl, and R_3 is hydrogen.

9. A method of treating the elevated intraocular pressure of a patient which comprises administering to said patient an effective amount of a compound having the formula:



wherein R_1 is:

$-SO_2NH_2$; $-S(O)_nR_4$; $-OR_4$; $-C(O)R_6$; aryl, heteroaryl, aralkyl, heteroaralkyl, aralkenyl or heteroaralkenyl having from 5 to 6 atoms in the aromatic moiety and 1 to 2 carbon atoms in the alkyl or 2 carbon atoms in the alkenyl moiety; alkyl, alkenyl or alkynyl having from 2 to 8 carbon atoms which can optionally be substituted with one or more hydroxy or carboxy groups

wherein R_4 is:

hydrogen; alkyl having from 1 to 6 carbon atoms or alkenyl or alkynyl having from 2 to 6 carbon atoms optionally substituted by dimethylamine; alicyclic having from 3 to 6 carbon atoms; lower carbalkoxyalkyl having 1 to 4 carbon atoms in the carbonyl moiety and from 1 to 6 carbon atoms in the alkoxy moiety; phenyl; $CH_3OCH_2OCH_2$; lower dialkylamino optionally further

substituted by dimethylamine; or saturated nitrogen-containing heterocycles containing from 5 to 7 atoms optionally substituted with alkyl having from 1 to 3 carbon atoms

and R_6 is:

alkyl, alkenyl, or alkynyl or alicyclic having from 3 to 6 carbon atoms; lower carbalkoxyalkyl; or $CH_3OCH_2OCH_2$-

and n= 0 - 2

R_2 is:

$-SO_2NH_2$; $-S(O)_nR_4$; $-C(O)R_4$; $-OR_4$; bromo, chloro; aryl or heteroaryl having from 5 to 6 atoms; alkyl having from 1 to 8 carbon atoms, or alkenyl or alkynyl having from 2 to 8 carbon atoms which can optionally be substituted with one or more hydroxy groups,

wherein R_4, R_5 and n are as defined above;

R_3 is:

hydrogen; alkyl of 1 to 6 carbon atoms; carboxy; lower carboxy alkyl; or phenyl optionally mono- or di-substituted with lower alkoxy, fluoro, chloro, bromo or alkyl of 1 to 3 carbon atoms; or R_2 and R_3 taken together form a ring fused at the 4-5 positions of the thiazole ring and are chosen from the group consisting of tetrahydrobenzene and tetrahydropyridine and can optionally be substituted by carboxylic acid or lower alkyl or benzyl esters of carboxylic acid, lower alkyl, or halogen;

provided that at least one of R_1 and R_2 must represent the sulfonamide moiety, $-SO_2NH_2$ and that R_2 cannot be chloro or bromo when R_3 is methyl, carboxylic acid or esters thereof, or unsubstituted phenyl;

and pharmaceutically acceptable salts and mixtures thereof.

10. The method of claim 8 which comprises topically administering said compound to the eye.

11. A method of treating the elevated intraocular pressure of glaucoma in a patient which comprises administering to said patient an effective amount of a compound according to claim 9.

12. The method of claim 11 which comprises topically administering said compound of claim 8.

13. The method of claim 12 which comprises administering a unit dosage of from 0.001 to 10.0 mg of the compound of claim 8 on a daily basis.

14. A pharmaceutical composition for treating a patient having glaucoma, by topical administration to the eye, which comprises an effective amount of a compound according to claim 1 in a pharmaceutically-acceptable carrier.

15. The composition of claim 14 comprising from 0.01 to 15% of said compound of claim 1.

16. A method of inhibiting carbonic anhydrase activity in a patient which comprises administering to said patient an effective amount of a compound according to claim 1.

17. The method of claim 16 which comprises topically administering to the eye said compound of claim 1.

18. The method of claim 17 which comprises administering a unit dosage of from 0.001 to 10.0 mg of the compound of claim 1 on a daily basis.

Statement under Article 19(1)

The amendments presented to the International Bureau under Article 19 are intended to remove the 2 compounds disclosed in the prior art cited in the ISR from the scope of the claims.

Additionally, the method of treatment claim 9 has also been amended to remove these compounds from the scope of the claim.

INTERNATIONAL SEARCH REPORT

In: ional Application No
PCT/US 95/04730

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D277/36 C07D277/80 C07D513/04 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 72, no. 11, 17 November 1950 DC US, pages 4893-4896, WILBUR H. MILLER 'Heterocyclic sulfonamides as carbonic anhydrase inhibitors' see the whole document ---	1,2,9-18
X	JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 18, no. 5, August 1981 PROVO US, pages 997-1006, RICHARD J. CREMLYN ET AL 'Some heterocyclic sulfonyl chlorides and derivatives' see pages 998,999,compound Vb --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 June 1995	26. 06. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
PCT/US 95/04730

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,2 994 701 (JAMESM. SPRAGUE ET AL) 1 August 1961 cited in the application see the whole document	1-18
A	EP,A,0 079 269 (MERCK AND CO. INC) 18 May 1983 cited in the application see claims	1-18
A	EP,A,0 070 239 (MERCK AND CO. INC) 19 January 1983 cited in the application see claims	1-18
A	GB,A,945 671 (MERCK AND CO. INC) 8 January 1964 see page 1,lines 10,50;claims	1-18

INTERNATIONAL SEARCH REPORT

I national application No.
PCT/US95/04730

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 9-18 are directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In. .tional Application No
PCT/US 95/04730

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-2994701		NONE		
EP-A-79269	18-05-83	US-A-	4386098	31-05-83
		AU-A-	9004882	12-05-83
		CA-A-	1184119	19-03-85
		JP-A-	58085877	23-05-83
EP-A-70239	19-01-83	AU-B-	556363	30-10-86
		AU-A-	8577582	20-01-83
		CA-A-	1185980	23-04-85
		JP-C-	1616977	30-08-91
		JP-B-	2039504	05-09-90
		JP-A-	58029778	22-02-83
		US-A-	4416890	22-11-83
GB-A-945671		NONE		